MARCH 1952

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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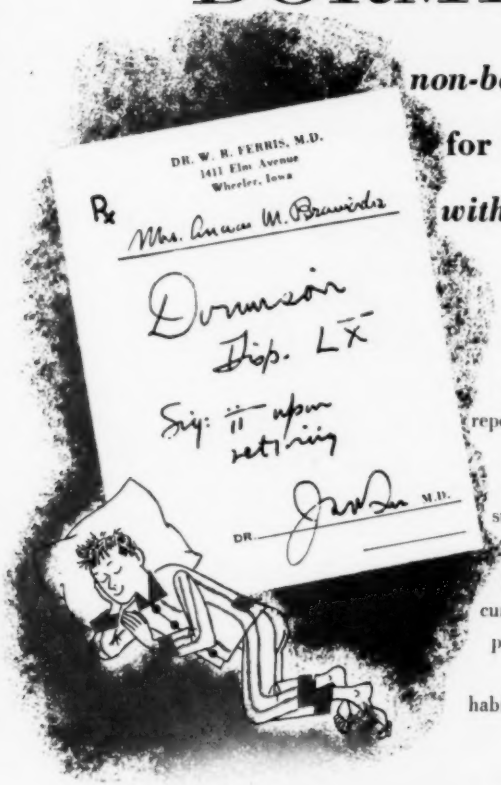

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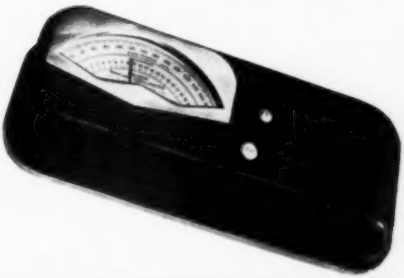

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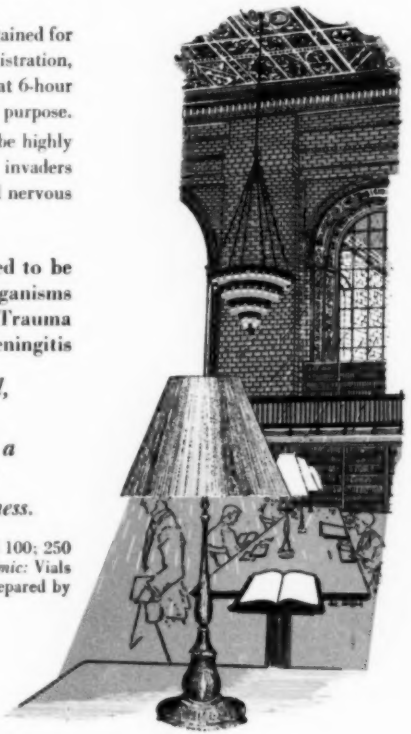

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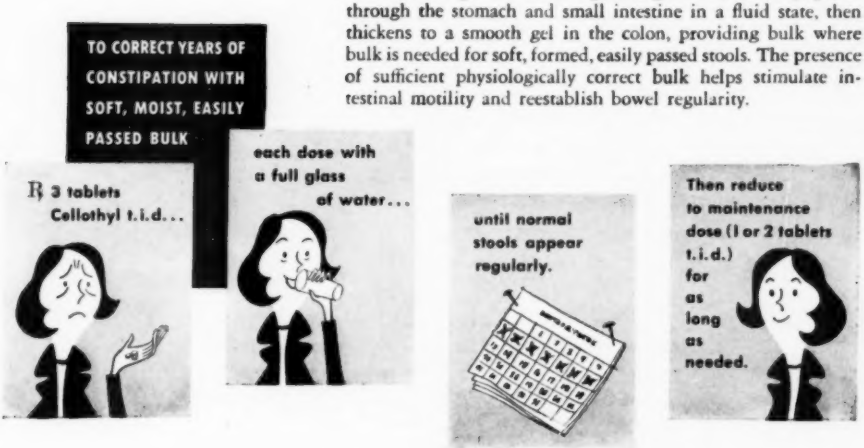
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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 28, NO. 3 MARCH 1952

PRESIDENTIAL ADDRESS*

WILLIAM BARCLAY PARSONS

President, The New York Academy of Medicine

It is now my duty to report to the Fellowship on the state of health of The New York Academy of Medicine. Full details will of course appear in the annual report, but this evening a few of the more noteworthy accomplishments of the past year will be outlined to you. I can assure you it has been a very busy and most fruitful year.

Health examinations of individuals cover the status of various organs, but in an institution the marks of health are accomplishment and progressive growth. Perhaps the same scale of values could be applied in the yearly examination of the individual; however that idea will not be developed as it is hardly germane to this particular discussion. It can be said, though, that the body of this Academy does consist of several organs, namely its committees and sections, with the central nervous system located in the Director's office and its heart in the Library.

During the past year the Library staff has been more than normally busy due to an increased use of the Library facilities, particularly marked in the photo duplication service but also with a real increase in the bibliographic, translating and editing services.

* At the Annual Meeting of The New York Academy of Medicine, January 3, 1952.

At least the usual number of exhibits have been prepared, such as Books by New York City Physicians in 1950, Medicine on the Battlefield before 1900, and From Heberden to Herrick in connection with the Graduate Fortnight last October.

The Library has been fortunate in receiving many rare and old books during the year, largely through the generosity of Friends of the Rare Book Room whose gifts have been published in the Academy Bookman. One of the examples of noteworthy memorabilia received during the year was that of the microscope, death mask and court uniform of Paul Ehrlich presented to us at a most enjoyable informal ceremony on December fifth by his daughter and two grandsons.

We have been able to make some gifts in turn, such as a collection of medical books of the period around 1840 for the doctor's office in the Farmer's Museum established by the New York State Historical Society at Cooperstown, and two copies of our Vesalian Atlas to most appropriate recipients: one, the University of Louvain Library which lost in World War I its priceless collection of Vesaliana and, in World War II, its copy of our Atlas, and the other to Dr. Willy Wiegand of the Bremer Press which printed the Atlas, all of whose copies were lost in the last war.

Three additions to the History of Medicine series published under the auspices of the Library have been authorized. One, a Bibliography of Articles on the History of American Medicine compiled from Writings on American History, 1902-1937, by the late Dr. Judson B. Gilbert, has been published, and the other two, Three Vesalian Essays by the late Dr. Samuel W. Lambert, Dr. Willy Wiegand and Mr. William M. Ivins, Jr., and the De Aneurysmatibus of Giovanni Lancisi translated by the late Dr. Wilmer Cave Wright, are in press and should be published in 1952.

The Committee on Medical Information has continued its bustling activity and has been extending the scope of its influence. As an example of the daily routine of service something in the neighborhood of thirteen thousand telephone inquiries were received and handled during the year, the largest number from doctors naturally but not far behind were the Press, individuals, and various organizations. Much correspondence was carried on, and many manuscripts and radio scripts were reviewed and releases furnished to the Press.

The Sub-Committee on the Laity Lectures exhibited their usual skill

and discrimination in selecting speakers for the sixteenth series on Medicine and Science and the seventeenth on Society and Medicine. The public welcomed and took advantage of their opportunity by attending in large numbers indicating that this activity is still a fruitful one.

This year the scope and content of the Postgraduate Radio program has been enlarged by cooperation between the Sub-Committee and the various Sections. This Sub-Committee has done yeoman service, has been able to secure financial and advisory help from generous friends and can look back with satisfaction on its labors because the response to this program has been most enthusiastic.

Of several conferences two this year were outstanding, the first on Panic was an all day and dinner meeting in which the basis for further conferences was established, and secondly the Eastern States Health Education Conference on the Epidemiology of Health was attended by 278 individuals, a really noteworthy achievement.

Five publications appeared this year under the auspices of this Committee: The Social and Biological Challenge of our Aging Population and the Psychological Dynamics of Health Education which were the collected papers of the Health Education Conferences of 1949 and 1950; Frontiers in Medicine, the Laity Lectures of 1949-51; Ministry and Medicine in Human Relationships, the transactions of the conference in 1950; and Tomorrow's Horizon in Public Health, the transactions of the Public Health Association of New York City conference in 1950.

Already plans are in hand for the coming year which are consistent with the zeal and industry of this Committee and which promise increasing contributions and widening of influence of the Academy through the activities of this Committee.

It has become customary to assume that the Committee on Public Health Relations will be engaged in many activities touching on municipal and state problems of public health. This year has been no exception in that sixty-three general subjects came under consideration with many subdivisions under the general term "Legislation." The annual report will go into considerable detail but the following topics have been selected to indicate the variety of problems tackled during the year:

The shortage of nursing personnel and the status of the practical nurse have been acute problems for several years. It is hoped that a start has been made in the solution of these matters. After a number of con-

sultations in well attended meetings with representatives of the Advisory Committee on Nursing Service of the Interdepartmental Health Council, the State and City Leagues of Nursing Education, the New York State Nurses' Association and the National Association for Practical Nurse Education, a set of recommendations was drawn up for consideration by the State Department of Education. These recommendations have to do with licensure, length of training, age of applicants and the development of schools for training practical nurses. The Committee is of the opinion that with the cooperation of various medical, health and hospital agencies these recommendations may be put into effect.

After a full inquiry into the evidence collected here and abroad on the inhibition of dental caries by fluorides, the Committee issued a report recommending that the City of New York be urged to proceed with the fluoridation of the public water supply, but that the Dental Service of the Health Department which is succeeding so admirably should be continued.

The tragedy of drug addiction, apparently on the increase particularly among younger individuals, led the Health Department, the Department of Education and some of the Welfare Agencies to request the Committee to organize a conference at which the medical aspects of drug addiction would be stressed as well as its sociological and cultural results. The material presented by outstanding experts in the field at an all day conference was so voluminous that it could not be properly considered at this session, so a second closed conference of longer duration is being called in the near future. Plans are being developed for publishing the transactions of this conference.

The Committee exerted its influence to help clear up the misunderstandings and near panic resulting from the sudden action of health departments in our own and other states in reference to the possible dangers of various inoculations for immunization during the poliomyelitis season. It has called attention to the unsound amendment to the Education Law of 1950 in reference to the study of health and hygiene in the Public Schools and recommended repeal thereof. The Committee also recommended to the Mayor and the City Council that the discrepancy in payments by the City to Voluntary Hospitals for care of the indigent should approach the cost to the hospitals for this purpose with the result that a moderate increase was authorized.

The report on a study of 750 neo-natal deaths and 250 stillbirths

begun early in 1950 has been completed and will be ready for the printers shortly. The purpose of this study has been to investigate the causes of such deaths and the possibilities as to preventability. This study was possible due to the generosity of the Commonwealth Fund, the Milbank Memorial Fund, the New York Fund for Children, the Association for the Aid of Crippled Children and the New York Foundation.

The most important contribution of the Committee on Medical Education was the preparation, organization and completion of the Twenty-fourth Graduate Fortnight that was held in collaboration with the New York Heart Association. The Subject "Disorders of the Circulatory System" struck a responsive chord in the profession because the lectures, panel discussions, clinics, exhibits and motion pictures were extremely well attended. Not counting the visitors to the exhibits over 8,000 admissions to the various exercises were counted. This includes representatives from twenty states outside of New York and nine foreign countries. The papers presented have been collected and will soon be in the hands of the printer.

It was with great regret that the Academy accepted the resignation of Dr. Mahlon Ashford for many years the Executive Secretary of the Committee on Medical Education. His great gift for organization, his quiet efficiency and his unfailing kindliness made his work with the Academy of the greatest value and endeared him to all with whom he came in contact. The success of this Post Graduate Fortnight was largely due to his brilliant flair for organization. We welcome his successor Dr. Robert L. Craig and can assure him of the wholehearted support of the Council and Fellowship of the Academy.

The main activities of the Trustees and Council have to do with finances and those matters referred by committees for approval. Last year we had the pleasant opportunity of presenting a scroll of greeting to the University of Glasgow in honor of its Fifth Centenary. The full financial report with the budget for 1952 will appear in the Annual Report. It gives me great pleasure to report to you this evening that our financial condition is excellent due to generous gifts from benefactors and a sound investment policy on the part of the Finance Committee with the aid of wise investment counsel. There was as you will see from the annual report a considerable amount of cash on hand at the close of the year which is being held as such awaiting a more advantageous moment for investment. The budget which includes a considerable in-

crease in salaries will show a sizable anticipated deficit. The Trustees and Council were of the unanimous opinion that an organization such as ours should not try to run on a balanced budget in good times or we will never enjoy goodly increases in capital.

This has been a successful year. The credit for this success goes to those individuals who have worked so hard for the benefit of the Academy and for all of us. These are the Chairmen and Executive Secretaries of the various Committees and those Committeemen who have given so unstintingly in time, thought and effort; Miss Doe and her staff in the Library; and last but over, behind and with all, Dr. Howard Craig, the Director of the Academy, whose genius keeps everybody happy and whose untiring efforts by example furnish the spark to the manifold activities of your Academy of Medicine.

THE EDWARD N. GIBBS MEMORIAL PRIZE

It is announced by The New York Academy of Medicine that a sum of $2,000 is available in 1952 under the Edward N. Gibbs Memorial Prize for original research in Diseases of the Kidney. This is a grant-in-aid and not for work already done.

Candidates must be physicians who have been graduated at least three years and are residents of the United States. They shall submit evidence of research already performed and protocols of proposed research upon the physiology of kidney function, etiology, pathology, or new methods of treatment of diseases of the kidney.

Applications with the required evidence should be mailed prior to April 15, 1952, and addressed to

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HUMORAL AND VASOMOTOR CONTROLS OF BLOOD VESSELS*

IRVINE H. PAGE

Director of Research, Cleveland Clinic, Cleveland

At the core of the problems of hypertension and shock lie the mechanisms which control the caliber of blood vessels. Whether blood pressure will be high or low depends on the content and caliber of arteries and arterioles and on their response to vasoconstrictor and vasodilator stimuli.

The three major groups of controls are the nervous system, the humoral system and the system controlling the ability of the blood vessels to respond to stimulation. The first two stimulate pressor or depressor responses but the latter regulates the degree to which response will occur. The total effect will depend, then, on the kind and intensity of the stimulus and on the responsiveness of the blood vessels.

The nervous control of blood vessels is a complex subject, grown so rapidly that it is too much to undertake in a limited discussion. I shall, instead, summarize contemporary knowledge of the humoral substances and forces which control reactivity.

HUMORAL CONTROL

All that is currently known is that a variety of pressor, depressor, vasoconstrictor and vasodilator substances exist in many organs. The part they play is little understood. They must be in some sort of equilibrium, just as are substances maintaining respiration.

Few of them have been characterized chemically and methods for their quantitative determination are inadequate. For the most part, it has been common custom to give a physiological phenomenon or a pharmacologically active extract a name and relax on the hypnotic effect thereof for some years. I refer, for example, to "urohypertensin,"

* Presented before the 24th Graduate Fortnight, of The New York Academy of Medicine, October 16, 1951.

From the Research Division of the Cleveland Clinic Foundation, and the Frank E. Bunts Educational Institute, Cleveland, Ohio.

"vagotonin," and the like. But there are notable exceptions. Who would have believed five years ago that the noradrenaline of the pharmacologist and the benzodioxanes of the chemist would be part of the common and necessary knowledge of the average internist?

Insofar as possible, the pressor and vasoconstrictor substances are divided according to their probable origin.

1. *Renal Origin.* Renin, a proteolytic enzyme, contained in tubular cells, acts on a protein, renin-substrate, to yield angiotonin or hypertensin. The substrate is a globulin which originates in the liver. The best evidence indicates that angiotonin is a peptide, though this is not established with certainty. So far, only biological assay of its pressor action is available for its semiquantitative determination. Despite valiant efforts by Taquini, quantitative methods for renin, based on angiotonin formation, are still inadequate. They do not give any clear idea of how it functions in the normal control of the caliber of the vascular system. Its isolation has very nearly been accomplished by Haas and Goldblatt in California.

Renin when injected into desoxycorticosterone acetate treated rats causes a syndrome like eclampsia (Masson, Corcoran and Page[1]). It has many other interesting physiological properties, such as eliciting diuresis, proteinuria and natriuresis.[2] Its several properties seem to qualify it as a presumptive central participant in vascular disease. This view is shared by our able colleagues in South America, Drs. Braun-Menendez and Fasciolo.

In my opinion there is more evidence in favor of the possibility that renin, and therefore angiotonin, is an integral part of the mechanism of renal hypertension than any other currently suggested substance. It should not be overlooked that Grollman and Drury especially, are of contrary opinion.

The "sustained pressor principle" of my colleagues, Helmer, Shipley and Kohlstaedt[3] has properties that suggest it has close relation but not identity with, renin. It acts almost exclusively in nephrectomized animals in which it gives a greatly prolonged rise in blood pressure. Whether it acts enzymatically to produce an effector substance is not known.

Vasoexcitor material (V.E.M.) of Shorr and Zweifach[4] is demonstrated in plasma by determination of the reactivity of metarterioles to topically applied adrenaline and the effect thereon of the injected test plasma. V.E.M. increases sensitivity to the adrenaline. Whether V.E.M.

affects the general circulation, and in what manner, remains to be determined. In certain phases of hypertension, plasma V.E.M. concentration seems to be greatly elevated.

A variety of pressor amines, e.g., hydroxytyramine, have been thought to be liberated from the kidneys in greater than normal amounts as a result of inadequate deamination. This thesis remains unproved and is currently receiving little attention.

The problem thus remains entirely fluid and current evidence does not justify ruling these substances in or out, either in the maintenance of normal blood pressure or in hypertension.

Pherentasin, presumed to be of renal origin, is a substance separated from plasma by Schroeder and Olsen.[5] They believe it to be an amine. It seems to be present in increased amounts in a few normotensives, and in practically all hypertensives' blood with the exception of those of "neurogenic" and "endocrine" origin and those with malignant hypertension. Schroeder finds large quantities only when some renal impairment is present. A good correlation between the presence of V.E.M., as demonstrated on the rat's mesoappendix, and the presence of hypertension and the occurrence of pherentasin was found. If it is true, as stated unequivocally by Schroeder[6] that the blood of patients with severe hypertension contains large quantities of pherentasin and a V.E.M.-like material as well, the problem of renal humoral agents is on the way to solution.

2. *Adrenal Origin.* The story of adrenaline and noradrenaline in relationship to nerve transmission and the pheochromocytoma has been told so often it needs no repetition here. The names of von Euler and Holtz, and later Goldenberg, Burn, Tullar and Holton have become associated indissolubly with this story. Some confusion exists in the use of the so-called "blocking agents" such as benzodioxane and tetraethylammonium as diagnostic tools, chiefly, I think, because enough attention has not been paid to their pharmacology. Under several circumstances, these agents may become pressor rather than exhibit their more usual depressor action.

Desoxycorticosterone-like corticoids are believed, chiefly as the result of the fine experimental work by Selye[7] to be intimately concerned in the production of vascular disease and hypertension. The evidence is largely from the effects of D.C.A. itself on uninephrectomized rats fed saline. Whether this applies to man remains to be investigated and we

shall await the results of work such as is being conducted by Dr. George Perera in New York and by Dr. A. C. Corcoran in our clinic, with great interest.

It seems unlikely that steroids are directly pressor, rather their action on the blood vessels is indirect. It remains to be proved whether the overproduction of D.C.A.-like steroids is primarily responsible for human essential hypertension, or if not primary, to what secondary degree they are involved. The hypertension of Cushing's syndrome with its adrenal cortical hyperfunction may have such a mechanism.

3. *Cerebral Origin.* Study of the effect of humoral agents on the vasomotor control of the brain and the liberation of vasoactive substance from brain and nerve has been but little prosecuted. Pressor substances have been detected in cisternal fluid and brain substance of human beings and animals but their chemical nature has not been elucidated. Pitressin seems to appear irregularly in cerebrospinal fluid.

It is of interest that stimulation of the central end of the cut vagus or sciatic nerve causes the liberation of a substance which can be transferred from the brain of the stimulated animal into a recipient, eliciting a large and prolonged rise in arterial pressure. The pituitary gland does not seem to be its source. Agents which reverse the pressor action of noradrenaline and adrenaline do not do so with this substance. Hydrazino phthalazine has been found to block its action.[8]

About fifteen years ago I separated a highly active pressor substance from cisternal and occasionally from spinal fluids.[9] Absence of the pituitary gland did not prevent its appearance. It was alcohol and water-soluble and not protein in character. Some of its pharmacological properties were those of adrenaline but others differed. Noradrenaline was not available at the time so no comparison was made. Raab[10] has recently also obtained good evidence that a sympathomimetic substance occurs in all parts of the human and animal brain. It has some chromogenic and pharmacologic properties in common with both adrenaline and noradrenaline.

Obviously it is impossible currently to evaluate any etiologic significance these substances might have. This does not detract from the intriguing investigative approaches offered by the occurrence of these materials.

4. *Uncertain.* For many years physiologists had known that when blood clots it also becomes vasoconstrictor. They also knew that to per-

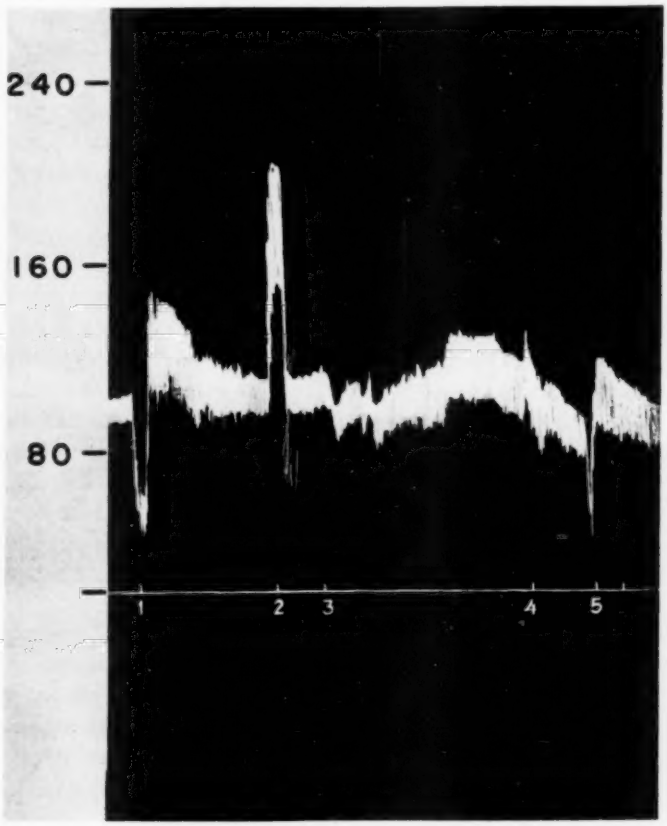

Fig. 1—Effect of 5-hydroxytryptamine injected intravenously into a dog with spinal cord cut at C_4. No anesthesia. (1) 5-hydroxytryptamine 100 μg. (2) Noradrenaline. (3) Infusion of Priscoline 5 mg/Kg plus Benodaine 3 mg/Kg started. (4) Noradrenaline. (5) 5-hydroxytryptamine.

fuse organs successfully it was necessary to insert a pair of lungs in the circuit. This problem was not of great import to us until we developed a rather elaborate modification of the simple Pissemsky ear perfusion with the object of determining the vasoconstrictor properties of hypertensive blood.[11] We could never be sure how much vasoconstriction might be due to undetectable coagulation, so the vasoconstrictor itself was studied.

Rapport, Green and Page[12, 13] reported in a series of papers the isolation, crystallization, partial structure and some pharmacological properties of the vasoconstrictor substance. Rapport[14] suggested that the substance might be a complex compound of equimolecular parts of creatinine, sulfuric acid and 5-hydroxytryptamine. The name serotonin was given the indole amine. This seems to have been confirmed by its synthesis by Hamlin and Fischer.[15] Dr. Hamlin kindly sent me 60 mg. of the synthetic material. It proved to be slightly more active than adrenaline as a vasoconstrictor in the perfused rabbit's ear vessels and about ten times less active than adrenaline as a pressor agent when injected intravenously into cats and dogs. This, among other properties, suggested that pharmacologically it was very similar to, if not identical with, the naturally occurring serotonin as shown in Figure 1.

There is little known about the function of this substance. Since it is liberated when blood clots, presumably it is concerned with the prevention of bleeding by causing the blood vessels to constrict down on the forming clot. It has some similarity to the pressor substance liberated from the brain on afferent stimulation.

The presence of adrenaline and noradrenaline-like substances in heart muscle (see Raab and Lepeschkin[16] for excellent review) and possibly in blood vessels, must have some significance, but currently it is unknown. Von Euler[17] concluded that the sympathomimetic actions of heart muscle extracts, as well as many other tissues, is due chiefly to noradrenaline. Raab and Lepeschkin[18] suggest that both adrenaline and noradrenaline elicit hypoxia of the heart muscle by chemically inducing an excessive and wasteful oxygen consumption in the myocardium, irrespective of coronary blood flow.

Depressor Substances

Depressor substances have for the most part been so poorly defined that the names so lightheartedly conferred on them are almost wholly unjustified. Almost nothing of their origin is known.

Histamine occurs in nerve tissue, in white blood cells, plasma and possibly red cells. So far no evidence has appeared that an abnormality of its metabolism exists in hypertension. Whether it aids in the maintenance of normal blood pressure is not known. Adenylic acid and adenosine are both active depressor substances but their association with humoral control of hypertension has not been adequately studied.

TABLE I—EXAMPLES OF THE RANGE OF NORMAL REACTIVITY (IN mm HG) IN DOGS

	Low	*Medium*	*High*
Adrenaline	4	30	72
Noradrenaline	20	73	118
Barium chloride	0	21	64
TEAC	−20	−43	−60
Veratrum	0	−31	−68
Azide	−26	−42	−64
Angiotonin	4	22	48

Acetylcholine is familiar as the mediator of parasympathetic nerve impulses, and like the previous substances, has not been shown as yet to be concerned in the mechanism of hypertension. Probably its concern with nerve transmission, especially in autonomic ganglia, give it a key position in control of vascular reactivity, as we shall see later.

Vasodepressor material (V.D.M.) has been identified as ferritin by Mazur and Shorr.[19] V.D.M. is believed to depress the reactivity of blood vessels of the rat's mesoappendix to adrenaline, to be significantly reduced in some stages of hypertension and to be greatly elevated in shock. Ferritin has not been demonstrated to affect blood pressure itself, nor does it depress the reaction of the arterial pressure to injected adrenaline or noradrenaline.

Carbon dioxide in some concentrations is a pressor substance while in others is a depressor. Unless the conditions are carefully defined, it is not possible to predict whether blood pressure will rise or fall on its administration. Being constantly present, it would be expected to be a controlling force in the regulation of blood pressure.

Clearly, investigation of depressor substances has but begun. It is hard to believe they are less important than pressor substances.

VASCULAR REACTIVITY

Substances believed to affect blood pressure by either cardiac and/or blood vessel stimulation have been cursorily reviewed. The assumption is always implied that these organs respond in a uniform fashion. The smallest experience in the physiology laboratory shows this to be untrue. Table I demonstrates average values for the responses of normal dogs

under pentobarbital anesthesia to standard doses of vasoactive drugs. The great spread is evident. We have studied the mechanisms of these variations in reactivity for a number of years and it is to this problem that we will now briefly turn.

Examples of the extremes of vascular reactivity occur in shock, where it is exceptionally low along with hypotension; after denervation of blood vessels where it usually is exceptionally high, along with labile hypertension, as in paraplegia. It should, however, be emphasized from the outset that there is no direct and obligate relationship between the height of arterial pressure and vascular reactivity. Reflection on the multiplicity of factors which control the height of blood pressure indicates why this must be true.

Control of Vascular Reactivity

1. *Neurogenic.* It is generally recognized that sympathetic denervation results in increased reactivity of blood vessels, a phenomenon extensively studied, especially by Cannon and Rosenblueth. There is no need to review this problem as it has already been done in masterly fashion by Rosenblueth.[20] Thus total dorso-lumbar ganglionectomy results in a very significant increase in blood pressure responses when such substances as adrenaline, noradrenaline, barium chloride and angiotonin are injected intravenously. In the following studies, I shall refer to this type of overall vascular response of the animal as a measure of vascular reactivity. Fortunately, for simplicity, the heart and blood vessels often parallel one another in their reactivity changes.

There are other ways of accomplishing much the same thing as surgical "total" ganglionectomy. Injection of tetraethylammonium chloride and hexamethonium are now widely familiar methods of eliciting ganglionic blockade. As we were able to show [21] after such blockade, reactivity rises immediately and greatly, just as it does several days after ganglionectomy. This suggests that changes in the humoral environment of the autonomic ganglia can exert a profound effect on the reactivity of the cardiovascular system, a concept almost wholly ignored in its relationship to vascular regulation.

If blockade causes increased reactivity, then would stimulation of autonomic ganglia decrease reactivity and is stimulation ever elicited by the usual constituents of the body?

We studied[22] this problem in curarized dogs breathing CO_2. A mod-

erate or sharp fall in arterial pressure occurred and almost immediately responsiveness to stimulation by chemical agents disappeared or was sharply reduced. It was as though the ganglia had suddenly rained down a shower of inhibitory impulses which blocked peripheral vascular responsiveness. Administration of tetraethylammonium during this period rapidly, but not wholly, restored responsiveness. But lumbo-dorsal ganglionectomy abolished altogether the ability of CO_2 to cause refractoriness. It is for such reasons that the ganglia seem so important a part of the neurogenic component controlling vascular reactivity.

Another approach to the problem consists in section of the buffer nerves, i.e., the carotid sinus and aortic depressor nerves, thus producing neurogenic hypertension. A curious change in vascular responsiveness occurs as a result. In normal and renal hypertensive animals repeated intravenous administration of tetraethylammonium chloride (TEAC) results in progressively lesser falls in arterial pressure until pressor responses occur. In contrast, dogs with buffer nerves sectioned show little or no tendency to reverse from depressor to pressor. Each dose of TEAC is followed by a sharp fall in blood pressure, each one like the other. The same reaction pattern has been found in some hypertensive patients as McCubbin and I found.[23]

In essence, we have interpreted this phenomenon as a change in the ability of TEAC to block sympathetic ganglia as a result of loss of the buffer nerves. It furnishes another example of the profound effect extraganglionic control may have on the ganglia themselves and thus indirectly on the reaction of the blood vessels.

We conclude that both the buffer nerves and CO_2, among other influences, may alter autonomic ganglia as indicated by changes in the response of the blood vessels.

The brain also seems to contain chemoreceptors which may influence the response of blood vessels (Taylor and Page[24]). Dogs were prepared by isolating the cerebral circulation completely from the body but leaving the nervous system intact, except for denervation of the carotid sinuses and bilateral vagus section. The brain was perfused by a donor dog. Substances injected either into the donor dog or directly into the arterial circulation of the brain could act only through the central nervous system of the recipient animal.

Injection of depressor substances such as histamine or acetyl choline elicited rises in blood pressure contrasting with adrenaline and noradren-

aline, which produced falls. Thus, substances usually considered pressor became depressor and vice versa when they acted directly on the brain. We have, therefore, concluded that the brain contains a system of chemoreceptors not heretofore described. The part they play in the overall regulation of the response of the circulation to stimulation remains to be determined.

The carotid sinus and depressor nerves have an important influence on reactivity but purposely I omit discussion of them until their actions are much better known and because they are now under active investigation in several laboratories.

There remains one more well defined component of the nervous control of the blood vessels. It consists of that outlying, intricate, chemical regulatory station, the myoneural junction, and its control of responses of vascular muscle. These receptors seem to be endowed with extraordinary properties but I shall consider only one as an example of how they may be influenced to affect vascular response.

Infusion of Benzodioxane, Dibenamine, or Regitine results in rapid inversion of the pressor adrenaline response to depressor and the slow inversion of that to noradrenaline. This occurs whether the vessels have central nervous connections or not. But the response to substances such as angiotonin, sodium nitroprusside, and barium chloride are unchanged. Clearly, it is possible to influence the vascular response in a highly specific fashion by substances which act at the myoneural junction. These junctions thus offer another point where vascular reactivity may be affected by what circulates in the blood.

2. *Humoral.* There are organs other than the nervous system that, having no direct connections with the blood vessels comparable to nerves, nevertheless influence their reactivity by humoral action. This whole complex regulatory system has not been recognized until very recently and has been little studied.

Nine years ago we investigated the responsiveness of blood vessels by injecting a variety of chemicals during the course of hemorrhagic and traumatic shock and later extended it to hypertensive animals.[25, 26] There was no doubt that as shock deepened, at first partial, then complete, vascular refractoriness appeared. Failure of blood vessels to respond has seemed a cogent reason for the failure of recovery in terminal shock. Indeed, to us it has remained one of the key problems of shock which has received no solution and relatively little investigation.

(a) *Liver.* Loss of this organ profoundly affects vascular reactivity in a fashion not unlike that which develops as shock deepens. For several hours after removal, it is normal, then despite treatment with whole blood, glucose and salt, reactivity gradually is lost and arterial pressure falls concomitantly.[27] We have so far found no way to restore reactivity or to prolong life. Whether the liver produces some substance vital to the mechanism for vascular contraction or must remove some noxious agent remains to be determined.

(b) *Kidneys.* It has been known for some time that bilateral nephrectomy intensifies the pressor action of renin and angiotonin. Other substances also may be augmented. There seems to be no direct relationship between the heightened reactivity and the concentration of retention products. As with the liver, it is not clear whether the destructive or excretory chemical functions of the kidneys are involved. Currently all we can say is that when dogs are kept alive by peritoneal lavage or the Kolff artificial kidney, the heightened responsiveness does not appear (Page and Kolff[28]).

(c) *Adrenals.* The extended studies on the effect of the adrenal glands by many investigators must be passed over with the statement that loss of the whole gland without replacement therapy gradually causes loss of reactivity. It is not of the degree seen after hepatectomy. Complete restoration is achieved by treatment with cortical steroids.

Although there is evidence to the contrary, we have not been able to demonstrate any clear effect of injected DCA on reactivity of normal or uninephrectomized-salt-treated dogs (Masson, Page and Corcoran[29]).

(d) *Thyroid.* Complete suppression of thyroidal function in normal dogs sharply reduces vascular reactivity (Page and McCubbin[30]) which is only partly restored by feeding large doses of thyroid powder. In both neurogenic and renal hypertensive dogs, athyroidism is associated with only minor changes in reactivity and no significant decrease in blood pressure. Even slowing of pulse rate in neurogenic hypertensive dogs, which occurred several months after suppression of thyroidal function, did not reduce arterial pressure.

(e) *Pituitary.* We studied vascular reactivity in dogs a number of years before and after hypophysectomy. The results showed no impressive changes. Even when there had been accompanying diencephalic injury followed by marked obesity, vascular reactivity fell off only moderately.

Arterial Hypertension

The response of the arterial pressure to a variety of drugs acting on different parts of the vascular tree may be employed to determine the contrasting mechanisms of chronic hypertension experimentally produced in dogs. The results in the types of hypertension studied suggest that the pattern of response depends on the state of the extrinsic regulatory mechanisms of the blood vessels rather than on intrinsic change in vascular musculature (Page and McCubbin[31]).

Contrasting with chronic experimental renal hypertension, greatly increased vasomotor function in chronic neurogenic hypertension causes increased peripheral resistance. Thus the response pattern to such drugs as TEAC, the hydrogenated ergot alkaloids and hydrazino phthalazine is very different in primarily neurogenic hypertension from other non-neurogenic varieties. Some patients also show this differentiation, suggesting primacy of neurogenic mechanisms. Obviously, the purpose of this method of study is to find response patterns in patients which correspond with those in animals in which the mechanism is known or ascertainable.

TEAC has been employed in interesting studies by Ferris and his associates Brust and Assali[32] to evaluate in patients the degree of neurogenic and humoral participation in blood pressure maintenance in normal and toxemic pregnancy. The results, so far, suggest predominance of humoral control in toxemia.

The body faces an extraordinarily complex problem in the distribution of blood according to need. It should not, therefore, be surprising that complex systems of control are employed. To unravel this complex and resynthesize it, the system must be artificially pulled apart and studied as though the components were independent of one another, a condition inconceivable in the whole animal.

Conclusions

Substances which seem likely to be concerned in the control of caliber of blood vessels are of renal, adrenal and nervous origin, while a few are of uncertain origin. The pressor agents are better characterized than the depressor, but surely the one group is no less important than the other.

Integrated with the system of substances which cause pressor and

depressor effects are those which control reactivity of the blood vessels; a highly complex system with widespread roots in the body. The nervous system, especially the autonomic ganglia, carotid sinuses and cerebral chemoreceptors, the liver and kidneys play important parts in this regulation. It is the interplay of stimulating and depressing forces acting on blood vessels of changing responsiveness which determines blood flow and pressure.

The relation of these investigations to clinical hypertension is somewhat obscure but that ultimately one will be demonstrated can hardly be doubted. Enrichment of knowledge of the basic mechanisms controlling blood pressure and blood distribution must at least equal those leading to empirical treatment of hypertension.

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HYPERTENSION AND THE CHANGES IN THE FUNDUS OF THE EYE*

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EACH case of arterial hypertension presents to the ophthalmologist the problem whether by observing the vessels and the changes in the fundus of the eye he can tell anything about the character of the hypertension, and about its progress and outcome. If we are to be in a position to tell about these things, we must be clear in our minds about a number of physiologic and pathophysiologic processes. 1) We must know the processes which cause observable changes in the retinal vessels in the course of hypertension. 2) We must know the mechanism which produces an increase in the blood pressure. This presupposes an understanding of how the normal blood pressure is maintained and regulated. 3) We must be able to separate the main forms of persistent hypertension. And, 4) we must have an understanding of the pathogenetic factors in the individual forms, in so far as the pathogenetic factors can be understood.

The processes which effect changes in the retinal vessels and in the retina in the course of hypertension are: 1) Aging; 2) arteriosclerosis; 3) arteriolosclerosis; 4) spastic contraction and its consequence — arteriospastic retinopathy. Aging is characterized by 1) Lessening of the elasticity of the vessel walls which become longer and wider; and by 2) a diffuse thickening of the intima. These changes occur in a moderate degree in old people, but are exaggerated in cases of long standing hypertension. The lessening of the elasticity of the vessel wall is shown by the tortuosity of the retinal vessels and the widening of the light reflex. The diffuse thickening of the intima cannot be seen in the course of the vessel, but is shown in places where the artery crosses a vein. Here the thickened artery hides a portion of the vein on each side of the red column.

Arteriosclerosis is characterized by a nodular thickening of the intima in an irregular distribution. The sclerotic plaques may be close

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together, but are individually nodular. They cause irregularities in the course of the vessel. Such irregularities in the course of the retinal vessels are the only visible manifestations of the arteriosclerosis there.

Arteriolosclerosis is a thickening of the walls of the small arteries and arterioles due to the subendothelial deposit of hyaline and lipoid in irregular segments of the vessels. It only occurs in cases of long standing hypertension, and only in certain organs. It is found in the kidneys in practically every case of chronic hypertension, less frequently in the spleen and the pancreas. It occurs also in the brain and in the retinal arteries. It is never found in the vessels of the trunk and limbs. In the retina the affected artery has the known copperwire and silverwire appearance.

Spastic contraction of the retinal arteries occurs in certain cases of hypertension and involves all the arteries. It causes a narrowing of the vessel which is especially noticeable in the secondary branches. With the constriction of the vessels certain changes occur which constitute arteriospastic retinopathy: 1) Dilatation of the capillaries with slowing of the blood stream in them, a hyperemia; such a hyperemia is difficult to see against the red background, but is visible in the optic disc which is more red than normal and on which tiny vessels, usually invisible, can sometimes be seen. 2) As a result of the capillary dilatation fluid passes through the capillary wall, resulting in edema of the retina. 3) At a certain stage, red blood corpuscles pass through the capillary wall, resulting in hemorrhages. 4) Cottonwool patches appear as a result of tiny infarcts, with the production of cytoid bodies in the nerve fiber layer.

The narrowed arteries, the hyperemia of the disc, the edema of the retina, the cottonwool patches and the hemorrhages indicate the acute character of the arterial constriction. When the constriction lasts for some time, hyaline and lipoid deposits appear in the deeper layers of the retina and are seen as sharply defined white exudates. In the macula they form the characteristic star figure.

These changes present two distinct fundus pictures: One, which is dominated by the spastic contraction of the arteries and the arteriospastic retinopathy. This picture may vary from a mild to an extremely severe degree. The second picture is one in which there is no spastic contraction of the artery and no arteriospastic retinopathy. Instead there are seen the signs of diffuse thickening and loss of elasticity of the walls of the arteries, of arteriosclerosis, and sometimes of arteriolosclerosis. Complications, such as closure of a venous or arterial branch, may occur

with either fundus picture but are not a necessary part of the picture. In what forms of hypertension do either of these fundus pictures occur?

Before this question can be answered it is necessary to understand the mechanism by which hypertension is produced. This necessitates a discussion as to how the normal blood pressure is maintained and regulated.

The Maintenance of the Normal Blood Pressure

As long as the cardiac output and the blood volume remain normal the blood pressure depends upon the resistance in the peripheral vessels. It is generally accepted that the resistance is in the small arteries and arterioles. However, in textbooks of physiology and in the writings of investigators in this field one does not find definite indications as to what vascular region of the body serves as an effector organ for the maintenance of the normal blood pressure. One gets the impression that all small arteries and arterioles in the body are involved. A consideration of the vessels in many areas of the body will convince one that this is not so.

For the purposes of maintaining the normal blood pressure a large number of small arteries and arterioles must be in a certain definite state of contraction. In the organs such as the kidneys, the heart and the brain, there are not enough vessels of this kind to maintain the normal blood pressure by themselves, or to influence the pressure by a change in the contraction of their vessels. Any influence that these organs may exert on the state of the blood pressure would have to be an indirect one, by reflexly influencing the state of contraction of the vessels in one of the large vascular areas.

In the limbs and trunk the muscles offer such a large area of small arteries and arterioles. However, these vessels are constricted in the resting muscles, with a minimum blood flow through them. They cannot contract in the interest of raising the blood pressure for they are already contracted. They dilate during muscular activity with an increase in the flow of blood through them which is 6 to 8 times the amount while at rest. In spite of the diversion of such a large amount of blood to the dilated vessels the blood pressure does not drop below normal. On the contrary it increases and this increase is brought about by a constriction of the vessels in the splanchnic area, helped by the increased output of the heart. In fact, constriction of the splanchnic vessels with a rise in blood pressure may occur even with the thought

of taking exercise before any actual movement has occurred. It is clear that the vascular area of the striated muscles which have to dilate with any movement of the individual, cannot serve as an effector organ for the maintenance of the normal blood pressure.

There is only one other area in which the volume of small arteries and arterioles is sufficiently great to act as an effector organ for the maintenance of the normal blood pressure. This is the area of the splanchnic circulation. Constriction of the small arteries and arterioles there is able to raise the blood pressure, independently of the state of contraction of the vessels in some other region. Dilatation of the splanchnic vessels causes a fall in blood pressure, no matter what the state of contraction of the vessels in other regions. An undue dilatation of the splanchnic vessels may cause such an accumulation of blood in these vessels as to endanger life, and this state cannot be counteracted by the constriction of vessels in other parts of the body. The conclusion is inevitable that the small arteries and arterioles of the splanchnic circulation by their state of contraction serve as the effector organ for the maintenance of normal blood pressure. These vessels have an especially thick wall, a rich supply of vasoconstrictor nerves, and the muscle fibers in the walls of the vessels are extremely sensitive to adrenaline which is the chemical mediator of the vasoconstrictor nerves.

Regulation of the Normal Blood Pressure

It is obvious that in as widespread an area as the splanchnic circulation the state of contraction of the countless small arteries and arterioles must be integrated and regulated if the normal blood pressure is to be maintained. Actually there is a four-fold regulation of the state of contraction of the walls of these vessels.

The first is the peripheral autonomous regulation by means of a constellation of electrolytes in the muscle fibers of the vessel walls. When the splanchnic circulation is completely separated from the central nervous system, the vessels gradually take on their own state of contraction as a result of the presence of these electrolytes.

The second regulation is by impulses from vasomotor centers via vasomotor nerves. Centers for vasomotor activity are located in the lateral horn of the spinal cord. By themselves they serve the integration of local vasomotor reflexes and, by themselves, these segmental centers are not able to integrate the elements maintaining the systemic blood pressure. They are themselves regulated from a medullary center, which

seems to be essential for the maintenance of the normal vasoconstriction in the splanchnic region. This is the third regulation.

A fourth, more purposeful degree of integration of the lower elements which have to do with the maintenance of the normal blood pressure, is located in the hypothalamus. It is especially the centers in this region which regulate any increase in the degree of contraction of vessels in the splanchnic circulation when such an increase is required, as for instance during exercise. And it is these centers which promptly reduce the degree of contraction in these vessels when such a contraction is no longer required. It is by means of impulses from the hypothalamic centers that any accidental and incidental increase in the blood pressure is promptly returned to normal. The normal variations in blood pressure, the normal lability, express the reactive ability of the integrating hypothalamic centers.

How does such a conception of the maintenance and regulation of the normal blood pressure help us in understanding the manner in which an increase in blood pressure is brought about?

Hypertension

If such a conception as I have outlined is true, then it is clear that any increase in blood pressure can only be brought about by a change in the state of contraction of the vessels in the splanchnic circulation. This I assume to be the manner in which every increase in blood pressure is brought about. The small arteries of the striated muscles do not participate in such a change, for they are always constricted when the muscles are at rest and dilate at once with muscle activity. The vessels of the kidneys, the brain and the eyes, also do not participate in the change of contraction when the blood pressure is increased, for they are not part of the effector organ for the maintenance of the normal blood pressure. Only the small arteries and arterioles in the splanchnic circulation are abnormally constricted, and by their constriction have increased the resistance to the blood flow, and thus produced an increase in blood pressure.

The arteries of the kidneys, the brain and the retina, as well as those of other organs, regulate their local blood flow according to the needs of the organ, independently of the state of systemic blood pressure. Normally they do this by local adaptations, with the blood flow rushing in under the normal pressure. When local regulation has to be effected with a blood flow rushing in under an increased pressure, it means more

local adaptations on the part of these vessels, more work for them and more wear and tear. In the course of years this makes itself felt in the arteries of the kidneys, the brain and the retina: 1) by undue thickening of the intima; 2) by a lessening of the elasticity of the vessel wall; 3) by the appearance of atherosclerotic plaques; and in long standing cases by 4) arteriolosclerosis.

When in a case of hypertension spastic contraction of the arteries in the kidneys, the brain and the retina does occur, it means an added change, in addition to the constriction of the vessels of the splanchnic region. For such an added change an explanation must be sought.

I have said at the beginning that certain cases of hypertension are accompanied by a spastic contraction of the retinal arteries and by the consequent arteriospastic retinopathy. It is therefore necessary to consider what cases of hypertension go along without the added constriction of retinal, cerebral or renal arteries, and what cases are accompanied by them. Thus we have to classify the cases of hypertension.

Classification of Hypertension

Persistent arterial hypertension occurs as:

1. Benign essential hypertension.
2. An intermediary group of cases of essential hypertension.
3. Malignant hypertension or the malignant phase of essential hypertension.
4. Hypertension of renal origin.
   (a) Diffuse glomerulonephritis in its various forms (acute, subacute, subchronic and chronic).
   (b) In some cases of the more uncommon forms of renal disease, such as amyloid contracted kidney, polycystic kidneys, periarteritis nodosa with involvement of the vessels of the kidneys, and in some cases of hydronephrosis and of pyelonephritis.
5. Hypertension of preeclampsia and eclampsia of pregnancy.
6. In pheochromocytoma, coaretation of the aorta and Cushing's syndrome.

The Goldblatt experiment: I am here concerned with essential hypertension and with renal hypertension, and I shall take the hypertension of renal origin first. To begin, let us view the Goldblatt experi-

ment. Constriction of the renal arteries in experimental animals to a sufficient degree produces an increase in blood pressure which may last indefinitely. It has been shown that a humoral mechanism is involved, with the production of renin in the kidneys. This is carried into the blood stream and acts with hypertensinogen in the blood to produce hypertensin, a vasoconstrictor substance which acts on the walls of the small arteries. It must be assumed that when the kidneys are not separated from their nerve supply a neural mechanism is also involved, although the humoral mechanism alone is effective when the kidneys are completely separated from the central nervous system.

The Goldblatt experiment has been studied from every viewpoint. When one reads the reviews on this subject, also those of Goldblatt himself, one does not find an explanation as to why constriction of the renal arteries is followed by an increase in blood pressure. Such an increase does not follow the constriction of other arteries, such as the splenic artery, the femoral arteries, and the aorta below the origin of the renal arteries. Why then in the case of the renal arteries?

The only answer to this question is to be found in the interpolation of the glomeruli within the arterial system of the kidney. The renal glomerulus, of which there are two million, is a filtration apparatus, dependent upon the systemic blood pressure for the exercise of its function. When the systemic blood pressure is reduced, filtration in the glomeruli is reduced, and at a certain low level of blood pressure, between 30 and 40 mm. of mercury, urine formation ceases. Glomerular filtration is a most necessary function in the organism. In any reduction of the intraglomerular filtration pressure, the body at once reacts by an increase in blood pressure. This is accomplished by neural reflexes, for the vessels of the kidney have a very sensitive neural mechanism, and by the production of renin and of hypertensin.

The increase in blood pressure can only be brought about by a constriction of the small vessels of the splanchnic circulation. But hypertensin diffuses through the whole systemic circulation and presumably acts to constrict the small vessels of many organs, including the kidneys, the brain and the eyes. With such a constriction renal changes are produced, and also arteriospastic retinopathy.

The Goldblatt experiment is an example of the manner in which hypertension is produced as the result of a reduction in the intraglomerular filtration pressure.

Renal Hypertension: On viewing the various diseases of the kidneys

which are accompanied by hypertension, it can be noted that each and every one of them is characterized by an actual or threatened reduction in the intraglomerular filtration pressure. The consequence is an increase in blood pressure brought about by a change in the effector organ for the maintenance of the normal blood pressure by neural reflexes from the kidneys. However, the humoral mechanism is also active, and the production of renin and hypertensin results in a constriction of the small arteries in other organs including the brain and the eyes. As a result, cases of renal disease accompanied by hypertension are also accompanied by cerebral symptoms and by arteriospastic retinopathy. The extent of such symptoms and the degree of severity of the arteriospastic retinopathy is dependent upon the suddenness of the constriction of the arteries. It is the sudden constriction of the cerebral vessels which is responsible for the severe headaches, and for the occasional convulsions in cases of acute glomerulonephritis. It is the sudden constriction of the retinal arteries which is responsible for the acute character of the arteriospastic retinopathy. When the body accomodates itself gradually to the arterial constriction, renal hypertension may exist with hardly any cerebral symptoms and with a minimum of arteriospastic retinopathy.

Arteriospastic retinopathy, varying from a very mild to a severe degree, is an accompaniment of cases of renal hypertension.

Essential Arterial Hypertension: The cases of essential hypertension constitute the greatest number of cases of hypertension. They occur in three clinical forms:

1. Benign essential hypertension, in which the fundamental change is in the state of contraction of the small arteries of the splanchnic circulation. There is no abnormal constriction of the arteries of the kidneys, the brain and the retina. There is no arteriospastic retinopathy and no renal insufficiency.

2. An intermediary group, in which in addition to the hypertension, there are also cerebral symptoms and arteriospastic retinopathy.

3. A malignant group, which comprises the cases with the malignant phase of essential hypertension, or malignant renal sclerosis. In this group, in addition to the changes in the contraction of the vessels of the effector organ for the maintenance of the normal blood pressure, there is a spastic contraction of the renal, cerebral and retinal arteries. There are cerebral symptoms, renal insufficiency and arteriospastic retinopathy.

Benign Essential Hypertension: When a case of benign essential hypertension is followed from its beginning, the first noticeable change is a greater lability of the normal blood pressure. At times the blood pressure rises higher than is usual and takes longer to come down to normal. This increased lability persists and with the passing of time the blood pressure returns less and less to normal and gradually has a higher base level. This greater lability is actually an exaggeration of the normal variations, and the individuals with such an increased lability are the hyper-reactors to the ice-water test. In time the base level of the blood pressure gets higher. When the systolic base level remains around 200 mm. or higher, and the diastolic around 110 mm. or higher, changes are brought about in the arteries of many organs, including the kidneys, the brain and the retina. These are the result of the activity of the vessels regulating the local blood flow against the higher blood pressure.

In the fundus of the eye there are then seen: Tortuosity of the vessels, widening of the light reflex, the hiding of the vein behind the artery, irregularities in the lumen of the vessels, and in some cases the presence of copperwire and silverwire arteries. However, there are no signs of arterial constriction or of arteriospastic retinopathy. There are also no renal symptoms and no renal insufficiency.

The problem involved is: What has happened to change the state of contraction of the small arteries and arterioles in the splanchnic circulation?

By the term essential hypertension is meant that the hypertension is not secondary to any renal disease, not compensatory to any reduction in the intraglomerular filtration pressure, and not due to any organic changes anywhere in the body. The only change is the altered constriction of the vessels of the splanchnic circulation, without any apparent cause.

However, there must be a cause. I have stated that the course of essential hypertension is initiated with a greater lability which is an exaggeration of the variations of the normal blood pressure. The question arises as to why this greater lability is not properly controlled by the higher diencephalic centers whose function it is to reduce promptly any unnecessary increase in blood pressure.

The only answer is that in these cases the regulating centers in the brain are gradually losing the ability to regulate the subsidiary centers and the degree of contraction of the splanchnic vessels in the service of the maintenance of the normal blood pressure. Such a weakening of

the central regulatory control, I assume to be an inherent inherited characteristic of certain individuals, as in the weakening of the central regulatory control in certain other diseases which occur on a primarily functional basis. There is no doubt as to the hereditary character of essential hypertension.

With the lessening of the central regulatory control the vessels of the splanchnic circulation are still under the influence of the vasoconstrictor fibers from the segmental centers of the spinal cord, and the suprasegmental center in the medulla. But these centers have not the proper dampening and integrating control of the highest center. The spinal centers have escaped control and are in a state of greater irritability, and an excess of uncontrolled neural impulses reach the vessels of the splanchnic circulation. The constriction of these vessels increases, and with it the diastolic blood pressure, and in consequence also the systolic pressure.

These two factors, the gradual weakening of the highest central control over the subsidiary centers and over the degree of contraction of the splanchnic vessels in the service of the maintenance of the normal blood pressure, and the excessive improperly controlled neural impulses from the spinal centers, are responsible for all possible variations in the increase of blood pressure in the course of benign essential hypertension.

That there is an excessive flow of neural impulses to the splanchnic circulation is proved by the reduction in the blood pressure which follows removal of the corresponding vasomotor nerves by means of a sympathectomy.

The Intermediary Group: There are a number of cases in which after years of hypertension there is found an arteriospastic retinopathy. The blood pressure is usually around 220 to 240 mm. systolic and around 120 to 140 mm. diastolic, with a lability in the excursions of the blood pressure. These patients usually have headaches, and arteriospastic retinopathy of a varying degree. However, they do not have any renal symptoms, there is no renal insufficiency and the non-protein nitrogen in the blood is not increased. By inference, there is no spastic contraction of the renal arteries.

As long as there is no renal insufficiency these cases do not belong in the group of malignant hypertension. I prefer, therefore, to classify them in a separate intermediary group, between the strictly benign and the malignant groups of cases. To repeat, these are cases of essential

hypertension with arteriospastic retinopathy, but without renal insufficiency.

In these cases, in addition to the change in the degree of contraction of the small vessels of the splanchnic circulation, there has occurred a constriction of the retinal arteries, and presumably also of the cerebral vessels. What has happened to cause the added constriction of these vessels?

I believe this can be answered as follows:

The segmental centers in the spinal cord, from which the vasoconstrictor nerve fibers reach the vessels of the splanchnic circulation, extend from the sixth thoracic to the second lumbar segments. The excess of improperly controlled impulses which flow from these centers indicates that these centers are in a state of irritability greater than normal. The assumption I make is: That this increased state of irritability irradiates to the upper thoracic segments of the spinal cord. From these segments preganglionic fibers go to the superior cervical ganglion, from where postganglionic fibers reach the vessels of the brain and the retina. When such an irradiation has occurred there is an added constriction of the cerebral and retinal vessels to a varying degree, with the occurrence of cerebral symptoms and of arteriospastic retinopathy.

Malignant Hypertension, or the Malignant Phase of Essential Hypertension, or Malignant Renal Sclerosis: There is a small group of cases of hypertension which from the beginning run a more severe course, and eventually became malignant. In this group the increased lability which ushers in the hypertension occurs earlier in life than in the benign cases. A high level of hypertension is reached comparatively early. The systolic blood pressure eventually reaches 250 mm. and more, and the diastolic 150, 160, 170 mm. and more. In these cases the proper hypothalamic control of the degree of contraction of vessels in the service of maintenance of the normal blood pressure is practically lost.

For years the arterial constriction is limited to the vessels of the effector organ for the maintenance of the normal blood pressure. As a consequence of the high blood pressure, changes in the vessels occur in many organs, including the kidneys, the brain and the retina. These changes are particularly marked in the kidneys, where there is a diffuse thickening of the intima of the medium sized vessels, and marked arteriolosclerosis of the small arteries. As a result a number of renal elements are gradually obliterated, with the corresponding loss of renal function. In the brain there is arteriosclerosis especially marked in the

basal arteries and arteriolosclerosis of the small branches within the brain. The arteriolosclerotic segments of the small arteries in the brain dilate to form miliary aneurysms. Blood enters the hyalinized walls of these aneurysms which eventually rupture producing small round hemorrhages within the brain, and causing also the larger and fatal ones. In the retina the changes in the vessels can be recognized by the signs which I have enumerated earlier.

In these cases the greater state of irritability of the segmental vasomotor centers spreads practically to all vasoconstrictor centers in the spinal cord. There is now a spastic constriction of the arteries of the brain, of the retina, and of the kidneys, and probably of other organs.

In the kidneys the spastic contraction of the vessels increases any renal insufficiency due to a previous loss of renal elements. Now the equivalent of a Goldblatt clamp has been added. As a result the humoral mechanism becomes active, renin diffuses into the blood stream, hypertensin is produced and the added constriction of the small arteries everywhere aggravates the original spastic contraction. Small arteries in the kidneys undergo necrosis of their walls, renal insufficiency is marked, the non-protein nitrogen in the blood is increased, and in most cases cannot be reduced to normal. The hypertension has passed into a malignant phase.

In the brain the arterial constriction causes an edema of the brain, and with it an increase in intracranial pressure. There is severe headache, with other cerebral symptoms, and the increased intracranial pressure manifests itself by papilledema.

In the fundus of the eye the picture is that of arteriospastic retinopathy added to papilledema, and to any vascular changes already present as a result of the chronic hypertension. However, the clinical picture may vary considerably.

Summary

1. The changes in the fundus of the eye in the course of hypertension present two distinct pictures: One, which is due to aging of the vessels, to arteriosclerosis and to arteriolosclerosis, and is the result of the excessive activity of the retinal vessels regulating the local blood flow against the increased blood pressure. The second fundus picture is that of arteriospastic retinopathy, and is the result of a constriction of the retinal arteries. In what forms of hypertension do these two pictures appear?

2. Every form of hypertension is brought about by an increased constriction of the small arteries and arterioles of the splanchnic circulation. These vessels constitute the effector organ for the maintenance of the normal blood pressure.

3. Under normal conditions regulation of the proper degree of contraction of the splanchnic vessels is effected by means of vasomotor nerves. These take their origin from vasomotor centers in the lateral horn of the spinal cord, from the sixth thoracic to the second lumbar segments. These centers together with the suprasegmental center in the medulla are subsidiary to centers in the hypothalamus. From the hypothalamic centers purposeful regulation by way of the subsidiary centers is effected in the direction of an increased or decreased constriction of the splanchnic vessels as required.

4. In cases of benign essential hypertension there is a gradual lessening of the regulatory control by the hypothalamic centers as a result of an inherent inherited characteristic. The decontrolled subsidiary centers in the spinal cord are over-irritable and overactive, resulting in an increased contraction of the splanchnic vessels and with it an increase in blood pressure. In the fundus of the eye there are seen the signs of the first fundus picture due to aging of the vessels, to arteriosclerosis and to arteriolosclerosis. There is no abnormal constriction of the arteries of the kidneys, the brain and the retina. There is no renal insufficiency and no arteriospastic retinopathy.

5. In the cases of the intermediary group of essential hypertension the greater irritability of the vasomotor centers in the lower thoracic segments of the spinal cord has spread to the vasomotor centers of the upper thoracic segments. There is now in addition to the hypertension, an added constriction of the arteries of the brain and of the retina. There are cerebral symptoms, and there is now seen in the fundus of the eye the second fundus picture, that of arteriospastic retinopathy.

6. In the malignant cases of essential hypertension there is practically a complete loss of hypothalamic regulation of the blood pressure, and the subsidiary centers in the spinal cord are correspondingly overactive. The increased irritability of these subsidiary centers has spread to all vasomotor centers in the spinal cord. The constriction of the renal arteries has set in motion the humoral mechanism with the production of renin and hypertensin. There is severe hypertension, increased intracranial pressure and other cerebral symptoms, and there is renal insufficiency. In the fundus of the eye there are seen 1) the arterial changes

of the first picture; 2) the arteriospastic retinopathy; and 3) the papilledema which is a manifestation of the increased intracranial pressure.

7. In cases of renal hypertension there is either an actual or a threatened reduction of the intraglomerular filtration pressure. In consequence there is an increase in blood pressure brought about by a constriction of the vessels of the splanchnic circulation. However, the humoral mechanism is also active, renin diffuses into the blood stream, hypertensin is produced and acts on the walls of the small arteries in many organs. There is constriction of the cerebral and of the retinal arteries with the production of cerebral symptoms and of arteriospastic retinopathy. Cases of renal hypertension are accompanied by arteriospastic retinopathy of a varying degree.

Conclusion

I have attempted to clarify the changes in the fundus of the eye in cases of renal hypertension and in cases of essential hypertension in its three forms. I believe that this is the way in which the ophthalmologist should look at hypertension and at the changes in the fundus of the eye in its course. And this holds true for every physician.

EDEMA AND DYSPNEA OF HEART FAILURE*

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THE chief symptoms of congestive failure are weakness, swelling and shortness of breath. All authors agree that weakness occurs because the heart cannot normally increase its output in response to the stimulus of exercise. There has been less general agreement as to the cause of the edema and dyspnea.

The amount of blood pumped per minute in patients in heart failure is less than that pumped under similar conditions by patients without heart failure. The separation of patients with heart failure into two groups, those with high output failure and those with low output failure, has caused considerable confusion. The cardiac output at rest varies considerably from person to person. In the same patient it varies greatly in different physiologic and pathologic states. Exercise, eating, apprehension and epinephrine increase the cardiac output; motionless standing decreases it. In a person with a normal heart the resting cardiac output will be decreased if the subject has myxedema, and increased if he has anemia, thyrotoxicosis, beriberi or arteriovenous fistula. There are no absolute levels of the circulation above which circulatory failure does not occur and below which it always occurs. The amount of blood pumped must be considered in terms of the immediate needs of the body rather than as an absolute value.

In the natural history of slowly progressive congestive heart failure it is the rule rather than the exception for symptoms to occur during periods when the cardiac output is above the resting level. Fatigue develops during the day when the subject is active. The output is increased above the resting value, but is below the level that is reached by a normal heart.

During sleep the cardiac output falls from a subnormal exercising level to a normal value for rest, and the output becomes sufficient for

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the resting needs, causing symptoms to disappear. As the heart becomes weaker, signs and symptoms of congestive failure persist at rest. In these patients the cardiac output is consistently below the resting value unless complicating physiologic or pathologic states are present.

Patients with advanced pulmonary disease, anemia, thyrotoxicosis, beriberi and arteriovenous fistula have a high resting cardiac output. In them circulatory failure usually develops before the resting cardiac output falls below the value for normal subjects. The significant fact is the fall in cardiac output to a value below that found in the diseased state in the absence of heart failure.

Stimuli which normally cause a rise in cardiac output frequently cause a fall in output in congestive failure. The reverse is also seen, and stimuli which cause a fall in the normal subject cause a rise in the patient with failure. Any stimulus, such as exercise or excitement, which normally increases the output may decrease the output in a fatigued heart. As fatigue increases the ability of the heart to empty decreases. Anything which decreases the activity of the patient and normally decreases the output may increase the output of the fatigued heart.

In uncomplicated heart failure which persists at rest, blood flow has been reduced in all areas where it has been studied.[1] The reduction in splanchnic blood flow and cerebral blood flow is proportionate to the decrease in cardiac output; the reduction in renal blood flow is much greater. Fasting splanchnic oxygen consumption is maintained at a normal level by widening of the arterio-venous oxygen difference. Cerebral oxygen consumption is usually normal but may be reduced slightly in severe failure. The reduction in blood flow to the various areas studied is related to the change in cardiac output and does not correlate with changes in venous pressure.

Edema in heart failure may be divided into two types: 1) that caused by a redistribution of fluid normally present in the body; 2) that caused by a gain in weight indicating an abnormal accumulation of salt and water. The first type, that produced by redistribution of normal fluid, is seen in pure form in patients who develop a massive infarct of the left ventricle without previous symptoms of heart failure.[2] These patients may rapidly develop massive pulmonary edema. Blood is pumped into the lungs by the right ventricle, and it is not removed by the left ventricle. The pulmonary capillary pressure rises sharply, and fluid is pushed into the lungs. Fluid enters the blood stream from the extracellular areas supplied by the systemic circulation, and thus becomes available

for increasing the pulmonary edema. The hematocrit reading and plasma protein concentration indicate a slight to moderate fall in blood volume. The weight of the patient is unchanged.

In the second type of edema, fluid is retained in the body and weight gain occurs. For some reason related to heart failure, the kidneys are excreting less water than the patient is drinking. The exact reason why the kidneys retain fluid has not been agreed upon.

In chronic heart failure there is a striking disturbance in the circulation to the kidney. The renal blood flow is reduced to a value only one-third to one-fifth that of normal and the glomerular filtration rate is reduced to a value one-half to one-third of normal.[3] This reduction in renal blood flow and filtration rate is related to the level of cardiac output, but shows no obvious correlation with the level of venous pressure. Tubular function remains good. The author believes that this reduction in filtration rate, secondary to the reduced renal blood flow in the presence of relatively well-functioning tubules, is the primary cause of the edema in congestive failure. According to this theory, the normal tubules are unable to depress their sodium reabsorbing function enough to allow the escape of large quantities of sodium in the urine when the amount of sodium presented to them is reduced to the degree seen in heart failure. This thesis emphasizes that the reabsorptive ability of the tubules in both normal subjects and patients with heart failure can be altered by various agents acting on the tubule, but it emphasizes also that the amount of sodium retention produced by these factors acting on the tubules is influenced in a quantitative rather than a qualitative way by the reduced filtration rate. In other words, both normal subjects and patients with heart failure retain sodium during light exercise, but the amount of sodium retained by the cardiac exceeds that retained by the normal subject. This quantitative difference is believed to be the result of the low filtration rate in the presence of reasonably well-functioning tubules.

Other investigators believe that the retention of salt and water is caused by a rise in renal venous pressure. Still others feel that a rise in systemic venous pressure causes loss of fluid into the tissue and that this loss of fluid from the blood stream in some way causes retention of fluid by the kidney. Many other persons think that the circulatory disturbance in the kidney is not very important, and that the sodium retention of heart failure is caused by the action of various hormones on the renal tubules. There is evidence that urinary corticoid excretion is

increased in heart failure.

Our chief difficulty in settling the question of edema in heart failure lies in our ignorance of the factors which control sodium excretion in normal subjects. We know that sodium excretion is increased on a high sodium intake and lowered on a decreased sodium intake. More sodium is excreted during the day than during the night. Lowering the blood volume by bleeding and motionless standing increases sodium retention. Cortisone and desoxycorticosterone cause sodium retention. Whether these hormones are important in the hourly and daily variations in excretion of sodium in normal subjects is not known.

In this discussion we have blithely assumed that the primary cause of cardiac edema is sodium retention and that retention of water and chloride are secondary phenomena. This is based on the clinical observations that 1) the sodium ion when given as bicarbonate, lactate or chloride increases edema formation; 2) chloride ion when given as calcium chloride or ammonium chloride does not increase edema; and 3) when sodium is rigidly restricted, patients with heart failure excrete water relatively well. In patients with sudden heart failure the concentrations of sodium and chloride in the plasma are normal. In many patients with chronic failure the sodium and chloride concentrations in the plasma are low. This has led many people to wonder if too much emphasis is not put on sodium retention, and they raise the question of whether in certain instances water retention may not be the primary defect.[4] Let us consider what we know about low sodium concentrations in the serum and about the regulation of water metabolism.

Data collected in many laboratories have shown a surprising number of patients with occurrence of low sodium and chloride concentrations in the plasma.[4-6] In any chronic illness, with or without edema, we are apt to find the plasma sodium below 120 mEq. Many of these patients have none of the signs of circulatory difficulty of the type we are accustomed to see in patients in addisonian crisis. Indeed, we may well blame our friends in endocrinology for making us believe that patients always appear acutely ill when the sodium concentration becomes low. We forget that the addisonian appears very ill not because the electrolytes are out of balance but primarily because his entire body homeostasis is upset by the lack of a functioning adrenal cortex.

These data indicate that in such chronic illnesses, the osmotic activity of the cells is decreased. In the past we have been taught that cellular osmolarity is rigidly defended, but the finding of low electrolyte con-

centrations in the plasma can only mean that the osmotic activity of the cell is also low. Cellular osmolarity can also increase as shown by observations after electric shock therapy.[7] These data are compatible with 1) retention of an abnormal quantity of water because of a disturbance in the mechanisms controlling water secretion, with subsequent dilatation of electrolytes; 2) lowering of osmotic activity of the cells so that water is retained by normal rather than abnormal function of the water-regulating mechanism. Any fluid-regulating mechanism which was set to fluctuate around the osmotic pressure of cells would give an invariable level of electrolyte activity in the plasma, but would regulate the plasma to correspond to the variable osmotic activity of the cell. This has been suggested by Welt et al. as a possible explanation for certain hyponatremic states.[7]

When a normal person drinks a large quantity of water, the level of electrolytes in the blood and extracellular fluid is lowered. The water passes into the cells to restore the osmotic equilibrium between intra- and extracellular fluid. This fall in electrolyte concentration acts on osmoreceptors in the area supplied by the internal carotid artery and causes an inhibition of secretion of the anti-diuretic hormone of the posterior pituitary gland (ADH). When the renal tubules escape from the action of ADH, absorption of water in the distal tubules is decreased and water diuresis occurs. If hypertonic saline is now injected intravenously, the electrolyte activity of the blood and extracellular fluid is increased and water passes out of the cells to restore osmotic equilibrium. Immediately the osmoreceptors respond to the cellular dehydration with stimulation of the post-pituitary gland to produce ADH. Tubular reabsorption of water in the distal tubule is increased, and the water diuresis is checked.

If ADH is supplied exogenously by giving pitressin repeatedly in small doses, water drinking results in a considerable increase in intra- and extracellular water, and the sodium and chloride concentrations in the plasma are considerably decreased. May not such a mechanism be the cause of edema in patients with heart failure and low concentrations of chloride and sodium? May not the water retention itself result in a secondary retention of sodium and chloride? We do not think so, because the administration of pitressin to normal subjects over a 24-hour period does not cause the characteristic retention of sodium, so typical of heart failure. Water is retained, but not the salt.[8]

Let us consider more closely the findings in chronic illness with low

sodium and chloride concentrations. The patients do not show signs of peripheral circulatory failure. If sodium chloride intake is increased, either edema occurs because of expansion of the extracellular fluid volume or the salt is excreted in the urine. In either instance the concentrations of sodium chloride may change little. If salt is restricted in the diet, the excretion in the urine becomes greatly reduced and the fall in concentration in the plasma is slowed down. If desoxycorticosterone or ACTH is given salt retention occurs, but this results in an expansion of extracellular fluid and not in a rise in concentration in the plasma. If water is given a diuresis occurs. If hypertonic salt is given intravenously the diuresis is broken. We thus have evidence of a new level around which function the osmoreceptors regulating pituitary ADH secretion function. These observations suggest that in chronic illness cellular osmolarity changes and, therefore, the concentration of electrolytes in extracellular fluids is altered. Water is not retained to dilute the electrolytes because of the over-activity of post-pituitary ADH. The pituitary mechanism functions normally, but it is working around a new osmotic setup.

We believe, then, that we have three common situations in which the serum sodium and chloride fall to low levels. Water intoxication is a fourth and rare cause. The most common situation is the one resulting from changes in cellular osmolarity. Administration of salt can only expand the volume of extracellular water. It cannot raise the concentration in extracellular water because this would cause cellular dehydration.

Less common is the acutely occurring low salt syndrome in which the concentration of sodium and chloride is low because of constant loss of sodium chloride from the body either from the gastrointestinal tract or through kidneys whose tubules are injured by disease or temporarily paralyzed by the influence of mercurial diuretic. The acute renal low sodium syndrome has the following characteristics: On a low sodium chloride intake, the loss in the urine is greater than the intake of salt. Regardless of the level in the plasma, this loss continues, and does not stop until death or anuria occurs. It cannot be prevented by the use of desoxycorticosterone or ACTH. It is eventually associated with peripheral circulatory failure. Giving hypertonic sodium chloride solution results in dramatic clinical improvement.

The third common low sodium syndrome is a combination of low cellular osmolarity and excessive loss of sodium from the body. Let us consider an example. A patient with chronic illness has been placed on

a low sodium intake. After a time he does not do well; the sodium concentration is determined and found to be very low. He is given a little sodium chloride intravenously with dramatic improvement. Repeat laboratory examination shows that the sodium has risen only a little and is still much below the normal value. More sodium is given. The patient does not improve further; the extracellular volume rises and clinical edema occurs. If one insists on treating such a patient until the sodium concentration returns to normal, death frequently occurs from drowning.

A fourth, but less common cause of low sodium syndrome is the fall in electrolytes produced by water intoxication. In post-operative patients who receive only glucose and water and who have lost some salt by sweating, a syndrome characterized by confusion, rise in blood pressure, and reduced urine output may occur. Sodium, potassium and chloride concentrations in the plasma are low. Hypertonic salt solution given intravenously results in dramatic improvement. These same findings are seen in patients with Addison's disease who are being treated with desoxycorticosterone. If they force water, stop eating and discontinue their extra salt, the syndrome of water intoxication develops. In severe congestive failure where marked discomfort is present, or where infection or pulmonary infarction has occurred, one may retain water because of the repetitive neurogenic discharge of post-pituitary ADH. Hypertonic saline in these patients usually aggravates the edema.

So much for generalized edema. The cardiac retains salt and water because the kidneys do not excrete sodium normally. The retained fluid is of normal tonicity as long as cell tonicity is normal, but will change as cellular tonicity changes.

The third great symptom of cardiac failure is dyspnea. The basis for cardiac dyspnea is the structural changes which occur in the lung as a result of heart failure. Characteristically, the left heart is more damaged than the right and blood accumulates in the lungs. The pulmonary capillary pressure rises. Early in the course of heart failure, any fluid retained in the body by the kidneys tends to be dumped preferentially in the lungs. This tendency may become less marked as advanced heart failure occurs, and both ventricles fail equally.

When the patient with congestive failure is dyspneic at rest, he is pumping more air in and out of his lungs than do normal subjects. His dyspnea is a combination of decreased breathing space and increased ventilation. The cause of the increase in volume of air respired has never been fully determined.

The overbreathing causes a fall in the carbon dioxide content of the arterial blood and serves to maintain oxygenation of the arterial blood. The fact that the increased breathing is essential to maintaining full oxygenation is easily demonstrated by the use of morphine. As the ventilation is brought to a normal level by the action of morphine, the arterial oxygen content decreases to a point well below the normal level.

It has been stated repeatedly that in many patients with dyspnea from heart failure, the arterial oxygen saturation is normal and that need for oxygen is not the stimulus for increased ventilation. It is true that the cardiac patient has nearly normal saturation and that the slight fall in arterial oxygen saturation characteristic of the cardiac has no easily detectable effect on the breathing of a resting normal subject. But can these data from the resting normal be applied to the dyspneic cardiac?

We know that a normal subject at rest can breathe 100 per cent oxygen with little effect on his breathing. If he is doing heavy exercise, however, breathing 100 per cent oxygen causes a sharp fall in ventilation. Will the cardiac patient's response to changes in oxygen tension be like that of the man at rest or like that of the exercising man?

Data collected by Hickam[9] show that the orthopneic cardiac has a sharp fall in ventilation when he breathes 100 per cent oxygen, and that this fall is much greater than will occur in normal resting subjects with a corresponding change in oxygen tension. The cardiac who is dyspneic at rest responds to minor changes in oxygen tension in a way similar to that of a normal subject doing heavy exercise. The mechanism for this increased sensitization to oxygen remains to be determined.

Cheyne-Stokes respiration is one of the dramatic clinical findings in patients with heart failure.

Pryor[10] has recently described one of the mechanisms responsible for this type of breathing. These patients have large hearts and a long circulation time. The irregularity in breathing occurs without any evidence of disturbance in the carotid sinus or respiratory centers. The breathing follows closely the changes in arterial blood gases and their response to a given change in arterial blood is a normal one. Coordination between the lungs and the medulla is lost because of the large sac of blood placed in the heart between the lungs and the medulla. Overbreathing does not affect the medulla until the entire heart is filled with aerated blood. When this red, overventilated blood reaches the medulla, apnea occurs. The blood entering the left side of the heart becomes ven-

ous as it perfuses through the motionless lungs, but the blood leaving the heart remains arterial until the entire dilated heart is filled with venous blood. When venous blood finally reaches the medulla, marked overbreathing occurs, but this can have no effect on the respiratory centers until the venous blood empties out of the heart. This is only one of the mechanisms for Cheyne-Stokes breathing.

The tools for a study of respiratory stimulation in various disease states are now available and during the next few years our knowledge of the mechanisms of dyspnea is certain to be greatly increased.

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CIRCULATORY RESPONSES TO LIFE SITUATIONS*

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It is an old story that changes in cardiovascular function accompany emotional reactions such as anger or excitement. If this were the whole story there would be little point in reiterating it here. Only if such changes are actually pertinent to cardiovascular disorders and disease is it worth our while to dwell on them. Tonight I would like to summarize for you experimental evidence on that point gathered in collaboration with Doctors Harold Wolff, George Wolf, John Pfeiffer, Ian Stevenson, Charles Duncan, Robert Schneider, John Flynn, Herbert Ripley, and Phillipe Cardon. From the studies of these and other investigators it appears that certain cardiovascular changes set in motion by stressful life experiences may very well throw an important burden on the heart and the blood vessels.

Such studies have involved measurement of accessible indicators of cardiovascular function from among the various possibilities which may be grouped as follows:

1. Mechanical design of heart pump—valves.
2. Fuel for work—composition of coronary blood and calibre of vessels.
3. Blood volume.
4. Extent of peripheral vascular bed.
5. Distensibility of peripheral vascular bed.
6. Resistance of peripheral vascular bed.
7. Blood viscosity.
8. Stroke volume.
9. Heart rate.
10. Blood pressure.

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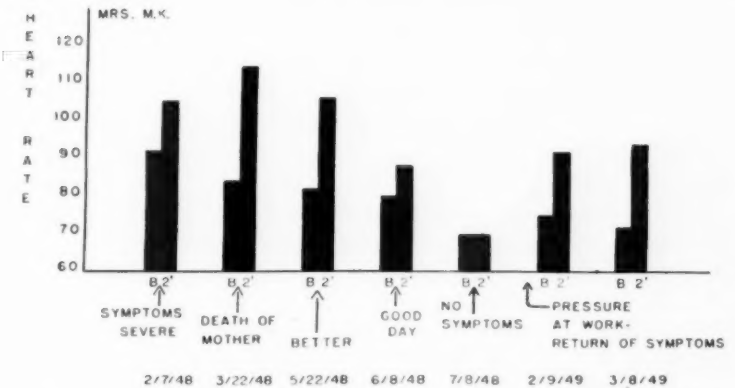


Figure 1—Repeated estimation of exercise tolerance under a variety of circumstances from day to day. The column above "B" represents the heart rate before exercise; above 2', the heart rate two minutes after the standard Master step test.

It has been shown that all of these functions that have been measured may become significantly altered during an individual's attempts to adapt to people and events in his environment.

Method: The various techniques and procedures involved in these studies are outlined in the original publications.[1-12] In general, the studies were carried out as follows:

Patients with various cardiovascular disturbances were collected and followed in a special clinic. They were studied with reference to background and life experience, attitudes and aspirations. These data were gathered from face to face interviews with the patient and other members of his family, from dreams, associations, slips of the tongue, gestures and behavior. A diary record was kept from day to day in which events, attitudes, and reactions were correlated with the occurrence of symptoms and cardiovascular disturbances. When such observations indicated repeatedly a temporal coincidence between events provocative of significant personal conflict and measurable changes in cardiovascular function, one had presumptive evidence that the two might be related. The validity of this suspicion was then tested in a short term experimental observation. Recordings were made during a control period of suitable length while the subject was relaxed and at ease. Then the topic of suspected conflict was introduced abruptly for

discussion. When the reaction to this maneuver included the sought for cardiovascular change, the evidence was considered to have been strengthened. After several minutes the "stress period" was terminated by strong reassurance on the part of the experimenter and attempts at diversion. When the disturbance could thus be "turned off" it could be fairly concluded that the life situation and the cardiovascular response were indeed connected.

Results: In Figures 1-10 are illustrated sample results of the studies on various indicators of cardiovascular function.

Heart rate and exercise tolerance: Figure 1 is a graph of repeated exercise tolerance tests performed on a 24 year old housewife who complained of palpitation, chest pain and dyspnea. Careful examination had failed to yield any evidence of structural heart disease or other abnormality. It was noted that the occurrence of tachycardia at rest and two minutes after exercise was closely correlated with what went on in her daily life. Her conflicts were concerned mainly with her relationship with her rigid, demanding, diabetic mother.

At her first visit exercise tolerance (Fig. 1) was considerably impaired. As the patient was followed in the clinic successive tests of exercise tolerance were made. The second test was made a few days after the sudden death of the patient's mother to which she reacted with considerable guilt and depression. Although the resting heart rate was lower this day the exercise tolerance was impaired more than on the previous day. During the interviews which followed the patient was able to talk more freely about her relations with her parents and brother. She gained some understanding of her emotional development and in addition was reassured concerning the condition of her heart about which her symptoms had given added anxiety. In the three months following the death of her mother the patient gradually improved and became free of symptoms. Exercise tolerance was then normal.

The patient remained completely well for another seven months. At this time she arranged for her husband to obtain a job at her factory, intending to resign from her own job and have a baby. Her boss, who had obliged by giving her husband a job, hinted that he would discharge her husband if she left the company. The patient felt frustrated and tense, but was unable either to express her feelings to the boss or leave her job. In this setting she had a return of the former symptoms in milder degree. Although her resting pulse rate was only slightly higher

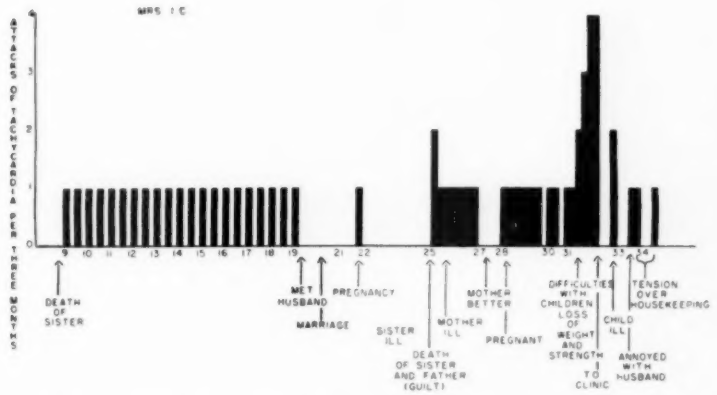


Figure 2—Diagrammatic representation of the frequency of attacks of paroxysmal tachycardia during the life of a 34 year old housewife.

than it had been, exercise tolerance was impaired and continued so for some months thereafter.

Heart rhythm—Paroxysmal tachycardia: Among the disturbances in rhythm which have been found to be correlated with the life situation is paroxysmal auricular tachycardia. The frequency of attacks over the period of the life of a 34 year old housewife is illustrated in Figure 2.

The patient's father was a house painter of moderate means. Both her parents were "worriers" and both enforced a rather rigid discipline on the children who were required to participate in the family duties and responsibilities at an early age. Notwithstanding fear of her father and awe felt for her mother, the patient described her family as a "close" one in which the members were intimately dependent upon each other. The patient said, "I think it was a happy childhood, but the sort in which one grew up before one's time." When the patient was 8 years old her eldest sister died after a long illness. Shortly after this event the patient had her first attack of tachycardia, and continued to have about two attacks a year until the age of 19. When she was 19 the attacks ceased soon after she met the man she later married. A few years thereafter she was faced with the responsibilities of pregnancy and she had a single attack during pregnancy. When the patient was 25 both her father and a sister to whom she was quite devoted died

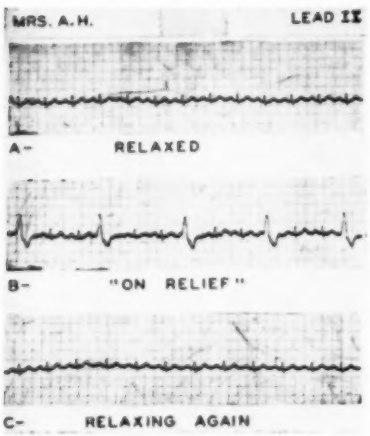


Figure 3

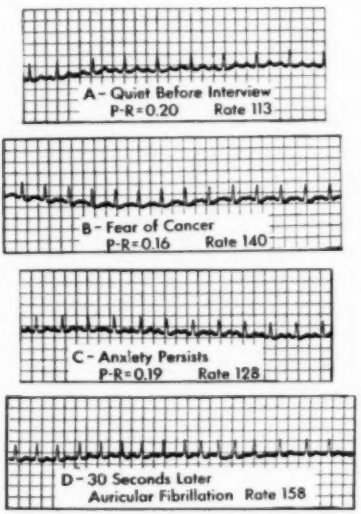

A - Quiet Before Interview
P-R=0.20 Rate 113
B - Fear of Cancer
P-R=0.16 Rate 140
C - Anxiety Persists
P-R=0.19 Rate 128
D - 30 Seconds Later
Auricular Fibrillation Rate 158

Figure 4

Figure 3—Abrupt occurrence of extrasystoles in a 55 year old woman during a discussion of pertinent personal conflicts.

Figure 4—Abrupt occurrence of auricular fibrillation during discussion of pertinent personal conflicts.

within a few weeks of each other. She bore the immediate shock well but a few weeks later began to be troubled by feelings of guilt toward her sister, whom she felt she had neglected. Her sister appeared frequently in her dreams. While brooding thus she had two attacks within a week and continued to have others during the course of a reactive depression her mother suffered. Attacks continued at about the same rate until, when the patient was 31, increasing tension and frustration in dealing with her domestic problems were associated with the increased frequency of attacks which brought her to the clinic.

Extrasystoles: The occurrence of extrasystoles during the contemplation of a stressful event is illustrated in Figure 3. The patient, a 55 year old woman complained of "nervousness."

The father of the patient was often depressed and her mother stern and domineering. The patient gave early evidence of anxiety as a child in frequent nightmares, nail biting and feelings of "nervousness" when in the company of her mother. She had planned a career in

music but at the age of 17, after the onset of bilateral chorioretinitis, abandoned it. She was by no means incapacitated by her inadequate vision and was able to get around easily and even to read large type. However, she did little for herself and subsided into a state of dependency upon her family, who, in turn, omitted her from the family councils and in general treated her like a child. After the death of her parents, a younger sister continued this practice, assumed supremacy among the siblings, handled all financial transactions, and freely directed the patient's life. In her thirties the patient became pregnant without marriage. Retrospectively at least, she felt that the man involved would have married her, but for the meddlesome interference of her family which drove him away. Her family urged her to allow the illegitimate child to be adopted, but she elected to raise him herself. This she did, not unsuccessfully, with the help of her family and some financial aid from the father. Relations with her sister continued to deteriorate and a few years before her first visit to the clinic palpitations began, associated with altercations with her sister. She finally withdrew from the latter's home and "went on relief." During an interview in the laboratory while connected with the electrocardiograph, frequent extrasystoles appeared as she answered the question, "How are you supporting yourself?"

Auricular fibrillation: Even such a major arrhythmia as auricular fibrillation was found to be related to stressful events in the life situation. An example is illustrated in Figure 4. The patient was a 39 year old housewife who had earlier undergone subtotal thyroidectomy for Graves's disease. At the present time basal metabolism rate was normal and, although she was presently complaining of excessive menstrual bleeding, there were no positive physical findings.

During the recording of the electrocardiogram the patient was interviewed. Heart rate was initially normal although accelerated. She expressed profound worries about her health. As she expressed fear that her menorrhagia was due to cancer, she became agitated and began to weep. Heart rate varied rapidly up to 140 and down to 128, then suddenly auricular fibrillation began.

Changes in electrocardiogram: During periods of significant conflict while discussing personal problems, a diminution in amplitude of the T wave of 0.5 mm. or more was recorded in 18 subjects of 35 studied with and without heart disease. Other changes noted are summarized in Figure 5. An illustrative tracing is shown in Figure 6 in which a

Electrocardiographic changes in 35 patients.	*No. of patients showing change during period of emotional disturbance*
A. Increase in heart rate.	
40 or more beats per minute	3
30 or more beats per minute	8
20 or more beats per minute	17
10 or more beats per minute	26
Less than 10 beats per minute	9
B. Changes in rhythm.	
All arrhythmias	9
Paroxysmal auricular fibrillation	1
Paroxysmal auricular tachycardia	1
Extrasystoles	8
Auricular	4
Nodal	2
Ventricular	6
C. Changes in electrocardiographic complexes.	
Diminution in amplitude of T wave of more than 0.5 mm.	18
Change in direction of T wave	8
ST depressions 0.5 mm. or more	4
ST depressions less than 0.5 mm.	2
P wave increased in amplitude	10
P wave decreased in amplitude	2

Figure 5—Summary of electrocardiographic changes observed during discussions of pertinent personal conflicts.

49 year old man was reminded of his anxiety about his heart. Such changes in the electrocardiographic complexes were very similar to those induced by exercise in individuals with impaired coronary circulation as shown in Figure 7.[11]

Blood Viscosity: In studies of changes in circulatory hemodynamics it has been customary for investigators to assume that blood viscosity will remain fairly constant for short periods in the absence of bleeding or serious trauma. In our own laboratory, however, Schneider,[8] using the viscosimetric method of T'ang and Wang, found that blood viscosity increased as much as 20 per cent in company with pressor response to a discussion of stressful topics. An example of such a finding is illustrated in Figure 8.

Renal Blood Flow: Another aspect of the circulation which has been

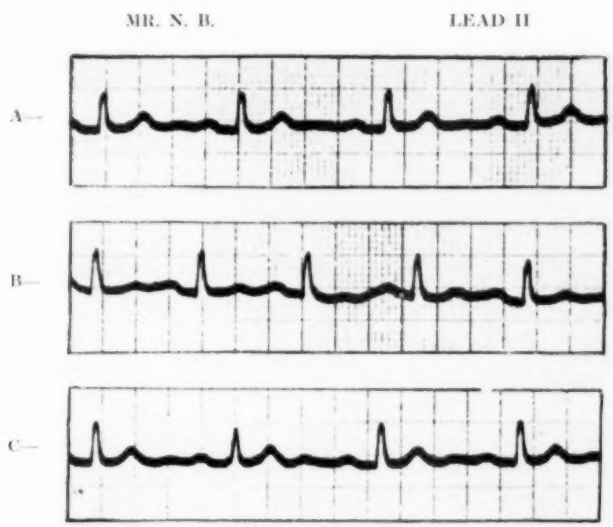
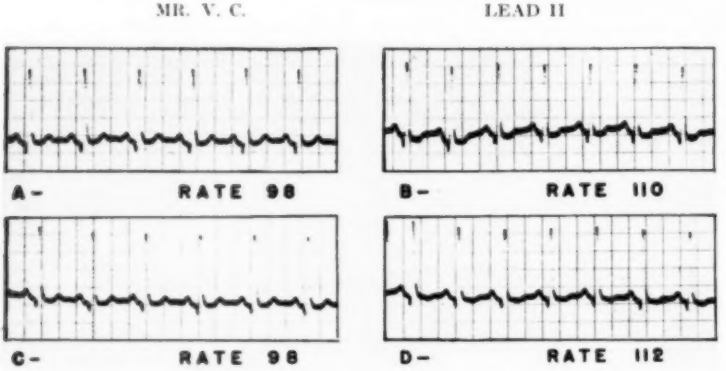


Figure 6—Depression of T wave in the electrocardiogram during a period of anxiety.

thought to be closely connected with disease, especially in hypertension, is the renal blood flow. Accordingly, 35 subjects with essential hypertension and 13 normotensive subjects were studied by the techniques of Homer Smith.[13] Effective renal plasma flow was estimated by clearance of para-aminohippurate and glomerular filtration by inulin-clearance.

The details of these studies have been reported elsewhere[2] but the prototype of the response is shown in Figure 9. Both hypertensive and control subjects whose blood pressure rose during the interview situation displayed evidence of renal vasoconstriction, with a sharp reduction in the effective renal plasma flow and an increased filtration fraction.

Comment: Such changes as these would only be important if they were capable individually or collectively of making the patient sick.



A—QUIET BEFORE EXERCISE.
B—ONE MINUTE AFTER EXERCISE.
C—SIX MINUTES AFTER EXERCISE.
D—TWO MINUTES LATER. ANXIOUS ABOUT HEART.

Figure 7—Similarity of electrocardiographic changes following exercise and during anxiety; note inversion of T wave in lead II.

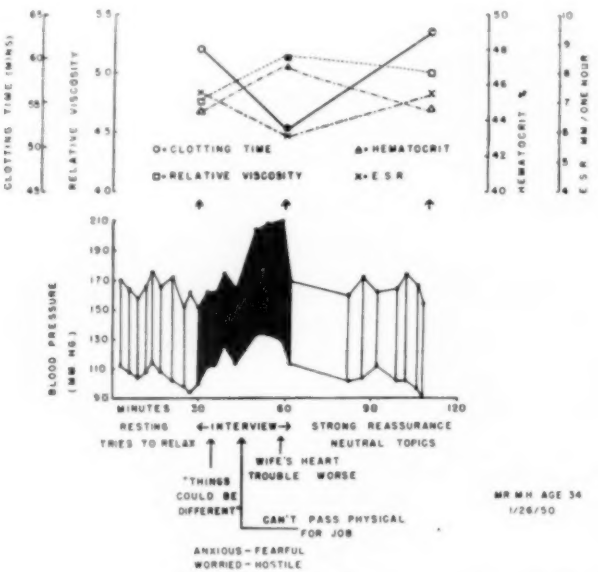


Figure 8—Increased blood viscosity and hematocrit associated with shortening of clotting time and sedimentation rate during a pressor response to a stress interview.

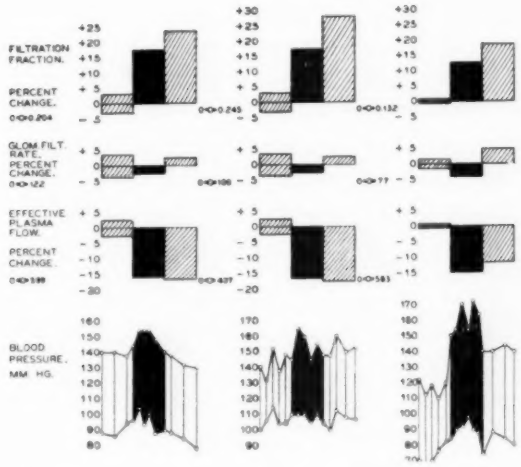


Figure 9—Changes in renal hemodynamics during pressor response to stress interview. The blackened sections represent the stress period, and the cross-hatching the control periods before and after interview.

Since the heart has a great reserve capacity to meet short term demands, it seems unlikely that any of these changes, when short lived, has any important significance.

To presuppose cardiovascular damage it would probably be necessary to demonstrate sustained and significant increase in cardiac work or interference with the nutrition of the heart or vessels.

The adequacy of cardiac nutrition may be reflected by the electrocardiogram but it is not possible to draw very sweeping inferences from examination of heart waves. With the ballistocardiograph and other tools, however, it is possible to get a rough approximation of relative differences in cardiac work.

General Hemodynamics: In ordinary stiff pipe pumping systems, the effectiveness of the circulation may be measured in terms of the efficiency of the pump and the actual work done. The effectiveness of the heart cannot be judged in these terms since it operates against a variable resistance and is required to fill a vascular bed of variable size. The adequacy of the heart in delivering blood to peripheral tissues depends directly on the quantity of blood pumped per unit time. The amount

$$\text{WORK} = \frac{7\,QR}{6} + \frac{WV^2}{G}$$

Q = CARDIAC OUTPUT
R = RESISTANCE IN AORTA
W = WEIGHT OF BLOOD MOVED (Q x 1.05)
V = MEAN SYSTOLIC VELOCITY

$$\left(\frac{\text{STROKE VOLUME}}{\text{Cross Section of Aorta} \times 0.34 \sqrt{\text{Length of Cardiac Cycle}}}\right)$$

G = GRAVITY CONSTANT

Figure 10—Formula for expressing work of the heart. "R", resistance in aorta, corresponds roughly to the mean blood pressure. Changes in "R" reflect changes in peripheral resistance when "Q", cardiac output, remains constant.

of work required to accomplish this job will vary not only with the demands of tissue metabolism but with the degree of peripheral resistance provided by arteriolar constriction or changes in blood viscosity. An increase in peripheral resistance will necessarily require more work of the heart and more oxygen consumption to maintain circulation.

The balance of tissue demand and work done by the heart can be illuminated by recourse to the underlying physical principles which relate work done to maintain flow through a fluid system to pressure, viscosity, cross sectional area and length of the conduit (Figure 10).

It is evident that a decrease in peripheral resistance increases the flow of blood to peripheral tissues if blood pressure is maintained, just as removing the nozzle from a garden hose increases the flow of water. As shown by the formula, if peripheral resistance is sharply reduced in company with an increase in cardiac output a much bigger job of flooding the tissues with fresh blood can be accomplished with comparatively little increase in actual work being done by the heart. If, on the other hand, peripheral resistance is increased, blood pressure rises and more work is required by the heart to meet tissue needs since delivery per unit time to the tissue depends upon output per unit of time by the heart. Thus, within the limits encountered in a well-compensated circulation, it is convenient and fairly accurate to consider that increasing stroke volume without an undue elevation of blood pressure is a relatively economical way to meet tissue demands while a rise in blood

$$\text{BLOOD PRESSURE} = \frac{\text{Length of Artery} \times \text{Viscosity} \times 8\pi \times \text{Cardiac Output}}{\text{Cross Section Area}^2}$$

Figure 11—Mathematical expression of Poiseuille's Law. Cross section area reflects the contractile state of the arterioles.

pressure without increased stroke volume is wasteful of energy and does not increase circulation.

This inference receives added support from the work of Evans and Matsuoka[14] with heart-lung preparations in dogs. Using the relationships contained in Poiseuille's Law (Figure 11), they noted that cardiac efficiency was greater when blood pressure was raised by an increase in stroke volume with peripheral resistance maintained the same than by an increase in peripheral resistance with stroke volume maintained the same.

These facts probably explain why vigorous and prolonged exercise is so well tolerated by a healthy cardiovascular system. It is well known that during exercise peripheral resistance is greatly reduced while stroke volume is increased. Our own experiments were performed with the ballistocardiograph immediately following 17 trips over the Master steps and at intervals of 5 and 10 minutes thereafter. While the ballistocardiograph may not be suitable for comparative determinations of cardiac output from individual to individual or even from day to day, it can reliably reflect relative differences in cardiac output in an individual subject when used more or less continuously in a single experiment.

Response to Exercise and Discussion of Exercise: Measurements at rest and following exercise in twenty hypertensives and twenty-eight healthy normotensive subjects are shown in Figure 12. Although the initial values in the two groups were different, the pattern of response was identical and included a sharp rise in stroke volume associated with a decreased peripheral resistance.

It was unnecessary for the subject to actually take exercise in order to invoke the "exercise pattern" of cardiovascular adjustment. Merely discussing the prospect of exercise with an individual who on previous occasions had undergone a double Master step procedure was sufficient to bring about the characteristic hemodynamic changes as shown in Figure 13.

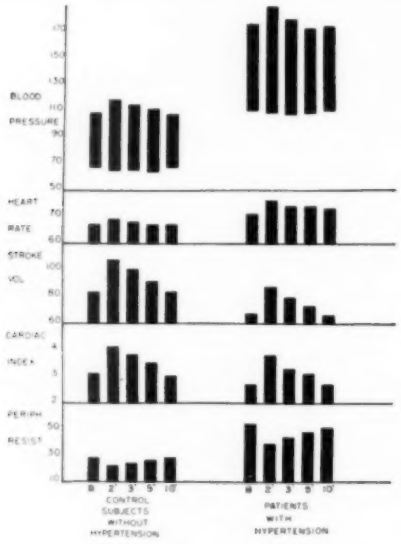


Figure 12—Hemodynamic changes before and after exercise as measured in normotensive and hypertensive subjects. "B" indicates before exercise, the numbers refer to determinations made 2, 3, 5, and 10 minutes after exercise.

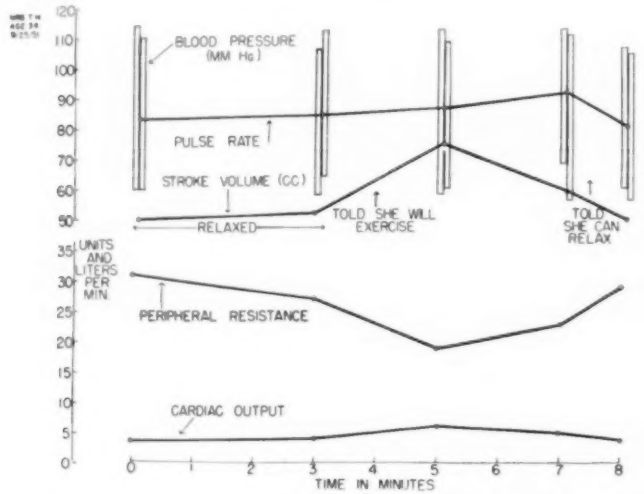


Figure 13—The "exercise pattern" of hemodynamic adaptation evoked in anticipation of exercise.

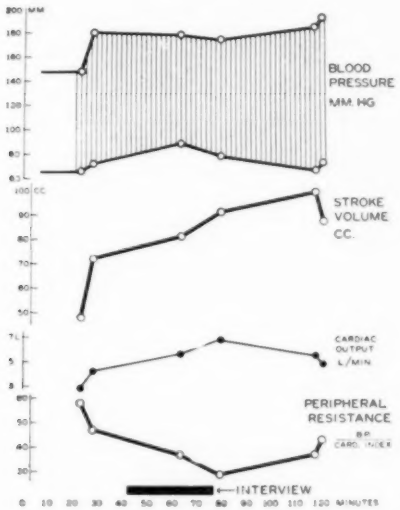


Figure 14—The "exercise pattern" of hemodynamic adaptation observed during a stressful interview.

The hemodynamic pattern of high cardiac output and low peripheral resistance can be maintained over long periods of time without damage to the heart since in Graves's disease cardiac enlargement and ultimate failure are rare and late complications.

In essential hypertension, on the other hand, where it has been shown that peripheral resistance is increased and cardiac output and peripheral blood flow are on the low side of normal,[15, 16] cardiac damage, enlargement and failure are the rule.

It became desirable to ascertain under what circumstances these contrasting patterns of cardiovascular adaptation could be induced. As already pointed out, exercise was uniformly associated with increased output and lowering of peripheral resistance.

Stressful Interviews: Observations were made on the effect of stressful life experiences without exercise. Data concerning the personality of each subject were derived from interviews with the patient and other members of his family, from associations, analysis of dream material and psychological tests. A further appraisal of attitudes and motivations

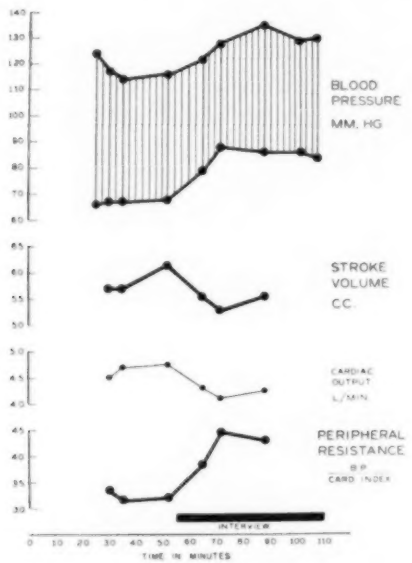


Figure 15—The "peripheral resistance pattern" of hemodynamic adaptation observed during a stressful interview.

of each subject was made by observation of his reactions especially during discussion of difficult life experiences, by things said and left unsaid, by gestures, slips of the tongue, blocking, projections and other indications in his behavior and stream of talk. These data were then correlated with the symptoms and with the measurements of circulatory functions.

The first striking finding was that the type of cardiovascular disturbance encountered during relatively overt emotional disturbances — the kind any observer could recognize — was similar to that seen with exercise, probably well tolerated by the body economy and of no significance in relation to disease (Figure 14). This may explain why obviously nervous patients with cardiac symptoms, so-called cardiac neurotics, live so long with healthy hearts. The cardiac overwork in increasing output is probably always short-lived because unless exertion is undertaken the peripheral blood supply will quickly exceed tissue demands, thus making the process a self limiting one.

The more costly pattern of cardiovascular adaptation was encountered when the patient subjected to significant emotional conflicts appeared calm and restrained and often altogether undisturbed (Figure 15). This pattern in which peripheral resistance is raised and cardiac output is not increased does not result in an increased supply of blood to tissues and can hence be maintained indefinitely without exceeding tissue demand so that this mechanism is self perpetuating. To put it another way, as long as peripheral resistance is high, the heart must continue to work harder than normal to maintain the same supply of blood to the tissues. This pattern of reaction to stressful interviews was characteristically encountered in patients with essential hypertension.

It was not characteristic of all hypertensive patients, however. The possibility suggests itself that those patients who live for years with high blood pressure without cardiac or vascular damage may be those who have adopted the more economical hemodynamic pattern of high output and low resistance. Since this pattern should be self limiting in view of the fact that tissue needs are being exceeded by the increased peripheral circulation, it may not actually be present all the time. Whether or not this pattern when adopted actually is intermittent is not known. Since one cannot know the blood pressure except when one takes it, it is not possible to draw inferences about an individual's day to day arterial pressure. Often the circumstances of attaching the sphygmomanometer cuff or merely being in the presence of the physician constitute an adequate stimulus to hypertension. For example, a 25 year old Armenian factory worker invariably had elevated blood pressure when the determination was made by his regular physician, a kindly but rather stern and quick moving individual. Even after intravenous injections of sodium amytal with strong reassurance his arterial pressure remained high as shown in Figure 16. When, on the other hand, another physician whom he considered more sympathetic took the blood pressure it was repeatedly and consistently much lower.

Even the so-called "standard" tests of blood pressure response are not valid indices of a prevailing hemodynamic state because the significance of the test often influences its effect on arterial pressure. For example, when one man, a 28 year old steam fitter, thought that the decision as to whether or not he would undergo a mutilating sympathectomy hinged upon the outcome of a cold pressor test, he displayed the response of a "hyperreactor." Later the same day, when he was reassured that the operation was not considered necessary, his blood

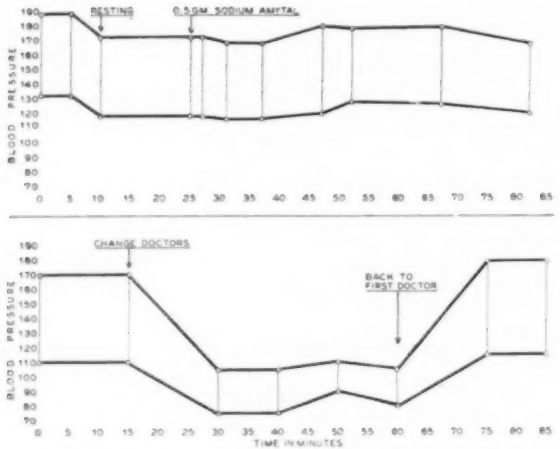


Figure 16—Effect of the prevailing situation on the level of blood pressure. Note the failure of intravenously administered sodium amytal to lower blood pressure in the presence of one physician. On another day, blood pressure falls to normal level without drugs in the presence of a second physician.

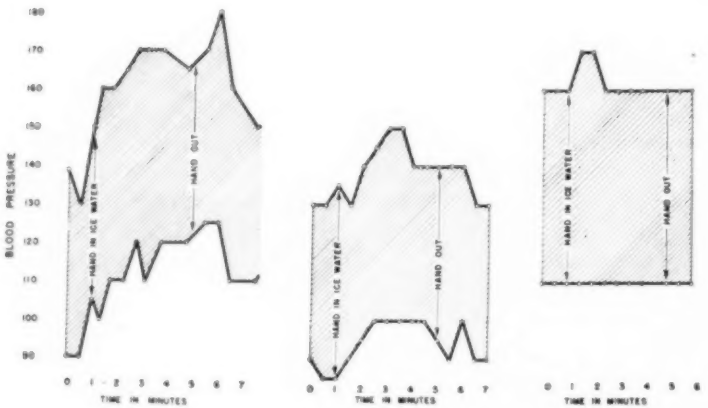


Figure 17—Variability of cold pressor response in the same individual. The first two tests were performed on the same day.

pressure was lower initially and the test produced a "hyporeactive" response. Even at times when his initial pressure was high, however, his response was "hyporeactive" when the performance of the test had no special significance for him (Figure 17).

Campbell and Blankenhorn[17] reported an interesting observation in 1925 which fits well this view of things. They found that certain hypertensives did not maintain their high blood pressure while they were asleep. These were the patients who had the least evidence of impairment of cardiovascular function. Schroeder and Goldman[18] also reported that the most benign cases of hypertension, those in whom Page[19] had earlier pointed out blotchy erythema and vascular lability, occurred in individuals who showed the most overt evidences of "nervousness" and "emotional lability."

On the other hand, the less evidently nervous, cautious and restrained hypertensive appears to be the one with the poorer prognosis. From our studies he appears to be the one who utilizes more readily the pattern of increased peripheral resistance with a slight fall in cardiac output.

These possibilities are under investigation at the present time. The answers are not available as yet. Suffice it, at present, to say that there are widespread cardiovascular adaptations to life stress, that these changes may be of the same nature and degree as those in response to other more concrete assaults from the environment and that thus they may turn out to be highly pertinent to the pathogenesis of organic cardiovascular disease. Certainly on the basis of the evidence at hand it behooves us as clinicians to accord serious attention to people and events, as well as other stresses in the lives of our cardiac patients.

What can be expected of this type of approach is, of course, not known. It hasn't been worked on very extensively and the results are hard to evaluate. Nevertheless, an illustrative story of one of our hypertensive patients may be relevant.

The patient was a 33 year old Jewish dealer in illicit merchandise whose hypertension had developed in a setting of conflict with a domineering and punitive mother. Against her will he had married an Irish Roman Catholic girl whose family equally disapproved of him. For more than a year they each lived at their respective homes. The patient felt unable to commit himself to the responsibility of a menage of his own. It was at this time that he was sent to us by his physician for consideration of sympathectomy because of sustained high levels of arterial pressure in the neighborhood of 170/120. Shortly after we began to

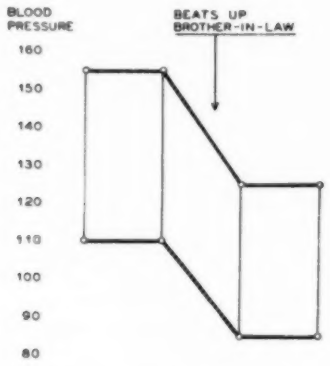


Figure 18—Abrupt fall in blood pressure following a relatively uninhibited expression of aggression.

follow him, his mother put him out of the home. He went to live with his in-laws under very crowded conditions. Here he became the object of repeated humiliations and verbal abuse, especially at the hands of one brother-in-law. During one of his visits at the hospital, he apparently got the impression that the author felt that it was unnecessary for him to continue quietly accepting this mistreatment. When he left the laboratory, where his blood pressure had been 155/110, he immediately looked up his brother-in-law and began to batter him with his fists. After giving him a severe beating he phoned the hospital and said, "Doc, I better come right in. My pressure is probably high enough to break the machine." He did come and his blood pressure was recorded at normal for the first time, 125/85 (Figure 18). Ultimately, as we worked with this patient, it was possible for him to reorient his attitudes to the point where his self confidence improved; he felt much less the need for restraint and he got a job, moved into an apartment of his own with his wife. He was by no means well but the pattern of his reactions had changed a great deal. His blood pressure was customarily within normal limits. Where formerly anger and frustration had been associated with not only a rise in arterial pressure but also an uncontrollable desire to eat, he now found that he lost his appetite when he was upset, and discussion of topics which had formerly induced a brisk elevation of blood pressure no longer were capable of doing so (Figure 19).

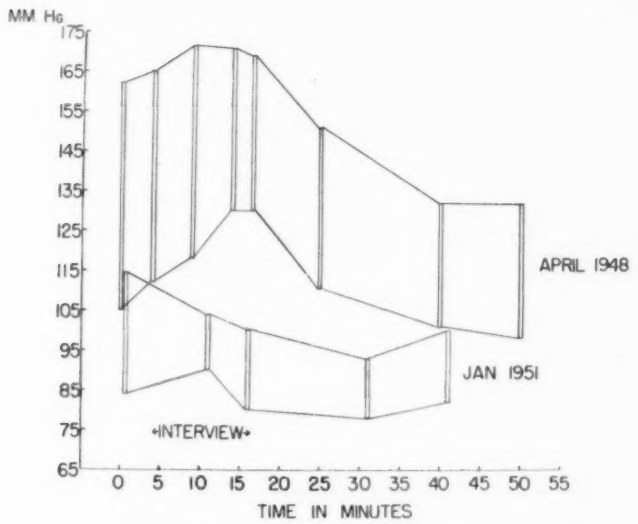


Figure 19—Change in reactivity in an individual after a three-year period. Initially, he was hypertensive and reacted to a discussion of personal problems with a brisk elevation of blood pressure. Later when he had lost evidence of hypertension and when his attitude had changed in a number of other ways, he no longer displayed a pressor response but actually showed a drop in blood pressure during discussion of stressful topics.

So I repeat what I said earlier. The data are not all in. The story is not complete but, from what we know at present, it is clear that the intelligent management of hypertension among other cardiovascular disorders includes attention to the patient as a person and his reactions to the stresses of day to day life.

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STATEMENT ON HOSPITAL MORBIDITY REPORTING*

Intelligent planning for the prevention of illness as well as for the care of the sick in a community depends upon an accurate knowledge of the extent of sickness. For many years health departments have gathered reports of communicable diseases to provide a basis for epidemiological studies. From time to time additions are made to the list of reportable diseases. These statistics, primarily designed to ascertain the prevalence and spread of infection, together with mortality statistics, are the only source of quantitative data regularly available for community planning for health.

Important as these two sets of figures are, they leave untouched a vast reservoir of illness. The reportable diseases do not include the conditions which cause the greatest amount of illness, and it has long been recognized that mortality figures do not give a true picture of the prevailing state of health. Each person dies but once, but he may have many illnesses, and it is the sum of these illnesses for the whole population that mirrors the state of a community's health.

Purposes other than the control of infectious disease may be served by the collection of general morbidity statistics. A community needs to know the extent of all its health problems in order to work toward their solution and to evaluate progress toward that goal. The operation of welfare programs, such as vocational rehabilitation, must be based on a knowledge of the extent of the need for such assistance. The present efforts to delve into the vast problem of chronic illness can be carried forward only if reasonably accurate information is available as to the number of persons afflicted. A relatively new use for morbidity figures has arisen from the development of hospital and medical insurance plans. Moreover, in the present world crisis the need to utilize the country's manpower to the best advantage suggests a need for employment of the handicapped, whose numbers and conditions must first be known.[1] Another aspect related to the uneasy world situation is that civil defense authorities must plan for health service in case of attack.

In England health authorities pressed for many years for a system of morbidity reporting, and several schemes are now in operation. So important was the health of the people during the recent war that beginning in 1943 a survey at regular intervals of representative samples of the population was initiated as a means of finding out how the general health was bearing up under wartime conditions. This plan has fulfilled its purpose so well that it is being continued in spite of financial strain. Recently an experiment in collecting hospital morbidity statistics has been begun for the express purpose of improving the efficiency of the institutions. All the teaching hospitals in England and Wales and hospitals of all types within a sample county and a sample city are sending records of their discharged patients to the central Register. It has been reported that this information is not only valuable for research, but has been of great help to the hospitals themselves in their teaching of medical students.[2]

Only rarely have attempts been made in the United States to ascertain the extent of disabling illness. In the federal censuses of 1880 and 1890, some information was obtained on a portion of the population, and conclusions were drawn, though with reservations because of the doubtful accuracy of the returns. In 1935-1936 the U. S. Public Health Service conducted a health survey covering about 2,000,000 people in eighty-three cities in 18 states distributed throughout the country.[3] Other than these, studies of the prevalence of illness have been made only in a limited number of areas and for special purposes.

Most sickness surveys have dealt with conditions at a point in time. The Committee on Public Health Relations in 1918[4] made one of the first which showed the prevalence

* Issued by the Committee on Public Health Relations of The New York Academy of Medicine.

of illness during a flow of time; it covered a period of one year. A similar study over more than two years was made by the Public Health Service in Hagerstown, Maryland, and published through the years 1926 to 1929.[3] Another was that in the Eastern Health District of Baltimore from 1938 to 1943.[6] Collins has recently made a comprehensive review of the various surveys.[7]

Although hospitalized illness is only a part of the total morbidity, it is a major part, the records of which may be of immense value to the community. As far back as 1913 Frederick L. Hoffman[8] published a monograph in which he demonstrated the practical value of hospital statistics, using material from Johns Hopkins Hospital for the period 1892 to 1911. In the hospitals of New York City there is a vast amount of information on illness, which could be made available without too great strain on the city's budget. When it is realized that nearly a million patients go through the city's hospitals annually and that another million are seen in outpatient departments, the potentialities of the mass of information in hospital record departments becomes apparent. A system of utilizing them may be the first step toward the development of a system embracing sickness data from other sources.

Efforts to use the morbidity information from the hospitals of this city have been made from time to time for many years. In 1913 the late Dr. Charles F. Bolduan[9] suggested a practical plan for gathering hospital statistics. This plan was not even tried out until ten years later, when the Hospital Information Bureau of the United Hospital Fund of New York made an arrangement with six general hospitals to cooperate in an experiment for a year or two.[10, 11] The method was found to be practicable, but it was never pursued farther. The only experience in New York City with the reporting of hospital data was a WPA project sponsored by the Departments of Health and Hospitals and carried out by the Welfare Council in 1933, known as the Hospital Discharge Study.[12] When the Hospital Council of Greater New York entered upon the preparation of its Master Plan for Hospitals and Related Facilities some twelve years later, these were the only data available to guide the Council in making its estimates of the needs for hospital service and other phases of the plan. From many points of view, the discharge study has amply demonstrated the value of a centralized system of reporting hospital morbidity statistics.

The Committee on Public Health Relations of The New York Academy of Medicine has for many years been interested in making available to the community its pathometric pattern, which is basic to public health and social planning. We recommended to the Department of Hospitals when it was first organized in 1929 that a morbidity reporting system be established for its own hospitals. A year or two later, when Dr. Greeff was Commissioner of Hospitals, a central hospital morbidity reporting office was established. Under the direction of Dr. Caroline Martin, it proved to be of much value in the administration of the municipal hospitals and it still continues with Dr. Marta Fraenkel as the director.

In 1948 the Committee on Public Health Relations of The New York Academy of Medicine joined with the Hospital Council and the Greater New York Hospital Association in recommending that the work of the morbidity reporting office in the Department of Hospitals be extended to all hospitals. It was understood that funds were available to set the plan in motion as of January 1, 1949. Subsequently we were informed that a cooperative office had been set up by the Department of Hospitals and the Department of Health and that before the system was installed in all hospitals, a pilot study would be made in three municipal and three voluntary institutions. In 1950 we provided professional advice to the central office on a summary list of diagnoses to be used in the coding of reports from the hospitals. For lack of funds, however, the experiment never got under way.

Prior to our taking up this matter anew with the Mayor and the Board of Estimate we learned that the Board of Trustees of the Russell Sage Foundation has made a grant which will enable the two departments to carry forward the project on an experimental basis.

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CLINICAL RESEARCH MEETING

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The New York Academy of Medicine will hold meetings Wednesday and Thursday evenings, April 23 and 24, 1952, at which investigators of New York City and vicinity may present results of original research in Clinical Medicine.

The Committee extends an invitation to all research workers of Greater New York and of neighboring cities within a radius of one hundred miles to submit an abstract of proposed presentation in quadruplicate, not to exceed five hundred words in length, to the Secretary of the Committee on Medical Education of the Academy not later than February 15, 1952. A formal invitation to participate in this program will then be extended by the Committee to the authors of papers selected for presentation.

THE LIBRARY PUBLICATION FUND COMMITTEE

JANET DOE

Librarian, The New York Academy of Medicine

While the atlas of Vesalian woodcuts, issued jointly by the University of Munich and the Academy Library, was in process of printing, it was realized that publications such as this would be costly to produce and would need very considerable subsidy. Dr. Samuel W. Lambert, Sr., the re-discoverer of the Vesalian woodblocks and the moving spirit in getting the new impression made of them, took the initiative in an effort to secure funds for publication expenses. He succeeded in raising nearly $16,000 and conceived the idea of setting this up as a "Library Publication Fund" which should become to some extent self-perpetuating. To accomplish this, the publication cost of a book would be met by the Fund and the returns from the book's sale would be restored to the Fund. In the course of time, then, a goodly portion of the money paid out would come back, and could be used in issuing another book.

This conception was an ingenious one and it has worked on the whole surprisingly well. The Fund has been able to finance the publication of Vesalius' *Icones anatomicae* in 1934, Janet Doe's *Bibliography of the Works of Ambroise Paré* in 1937, Arnold C. Klebs' *Incunabula scientifica et medica* in 1938, Wilmer Cave Wright's translation of Ramazzini's *Diseases of Workers* in 1940, Philip Van Ingen's history of The New York Academy of Medicine in 1949, and Judson B. Gilbert's *Bibliography of Articles on the History of American Medicine compiled from "Writings on American History" 1902-1937* in 1951. Now in press are two other volumes more fully described below: a translation of Lancisi's book on aneurysms by Dr. Wright and three essays on Vesalius by Dr. Lambert, Dr. Willy Wiegand, and Mr. William M. Ivins, Jr.

In addition, the Fund has had charge of the remaining copies of several other books: Dr. Wright's translation of Fracastorius' *De contagione*, 1930; Robert H. Halsey's booklet on the establishment of vaccination in America by Jefferson and Waterhouse, 1936; Martha Ornstein's *Role of Scientific Societies in the Seventeenth Century*, second edition, and Breasted's translation of the Edwin Smith surgical papyrus. Altogether, then, the Fund has fulfilled in no small degree the hopes with which Dr. Lambert launched it.

Perhaps a few words about some of the earlier publications will not be amiss here. In 1543 when the first edition of Vesalius' *De humani corporis fabrica* appeared, an interest in scientific illustration was awakening. Leonardo da Vinci's anatomical drawings had not been published, but Estienne was at work, and already the little volume by Canano had been printed with well executed engravings of the bones and muscles of the arm. The woodcuts in Vesalius' work, however, showed no transitory state, no groping for realism, but were superb and handsome illustrations exciting alike to artists and anatomists. The tradition of art and anatomy is an old one, for artists must perforce study the human body. Over the centuries many large anatomical atlases have come from the presses, showing the parts of the human body in woodcuts, engravings and lithographs, but no one volume has ever received the well deserved acclaim and respect given Vesalius' great work. It is for this reason that the discovery by Dr. Lambert of the existence of the original woodblocks was an event of unusual interest. Little persuading was necessary to convince others that a book containing cuts pulled from these blocks would be of importance in the history of art and medicine. This was a fortuitous decision, for with the second World War came the destruction of the blocks. The *Icones* in-

cludes woodcuts made from all the blocks then surviving, together with collotype reproductions of the 50 or so that were not found, a facsimile of the *Tabulae sex* (the six anatomical tables of 1538) and reproductions of the three drawings which some have thought to be the original of the frontispiece. It forms thus a definitive presentation of the graphic contributions made by Vesalius and his artist to anatomical study.

Dr. Klebs' book was compiled because he believed that the intensive study of incunabula as such had "hindered to no small extent the consideration of their function as literary documents, as carriers of human thought and emotion." As a beginning of this latter study, he undertook to list the earliest printed books in the fields of science and medicine, since it was his idea that in these works the "new mechanically oriented mentality" of the men of science could be profitably studied. His list is a frank first attempt to cite in one place in their various editions all the scientific incunabula he could trace, as a tangible basis for future criticism and emendation. It forms a valuable and unique reference tool for students of the early history of medicine and of printing. The list, appearing first in volume four of *Osiris*, was issued immediately also in reprint form as No. 1 of the Academy Library's "History of Medicine Series," the reprint now unfortunately being out of print.

Ramazzini's famous disquisition on occupational diseases marked the first attempt to recognize and discuss systematically the afflictions resulting from working conditions. No complete English translation of Ramazzini's enlarged second edition existed, and Dr. Wright, seeing the importance of this book in the light of modern concern with industrial diseases, determined to produce a faithful rendering. Presenting the Latin and English texts on opposite pages, the book is readable for its information and convenient for detailed study. Unfortunately it is now out of print.

Ornstein's *Role of Scientific Societies* constitutes a second edition and is the third printing of the author's Ph.D. thesis. It portrays the part played by scientific societies in the intellectual revolution resulting in the immense scientific discoveries of the previous three hundred years. James Harvey Robinson, in his foreword says, "So far as I know, there is no other work which can bring so many edifying reflections into the mind of the scientific worker and at the same time give the intelligent layman so correct a notion of the manner in which our modern science got under way."

Fracastorius is less well known as the author of his *De contagione* than as the composer of his poem on syphilis. His real contribution to syphilography, however, was the three chapters on this disease in this prose work, published sixteen years after the poem. Fielding H. Garrison has said of this book, "His work contains the first scientific statement of the true nature of contagion, of infection, of disease germs and the modes of transmission of infectious diseases. . . . He seems, by some remarkable power of divination or clairvoyance, to have seen morbid processes in terms of bacteriology more than a hundred years before Kircher, Leeuwenhoek, and the other men who worked with magnifying glass or microscope." The Latin and English text presented on opposite pages makes comparison easy.

The Edwin Smith papyrus has been called "the oldest scientific book in America and the oldest nucleus of really scientific knowledge in the world." Presented to the Academy Library in 1947 by its joint owners, the New York Historical Society and the Brooklyn Museum, it is made up of twelve sheets of beautifully inscribed and preserved papyrus. It is a transcription made about seventeen hundred years before Christ from a much older work, some twenty-three hundred years earlier. Prof. James H. Breasted published the translation of the papyrus in 1930, to produce which he had to render the ancient hieratic Egyptian writing into hieroglyphics before it could be put into English. The remaining copies of this magnificently printed book were given to the Academy along with the papyrus itself and have since been in charge of the Library Publication Fund, the last copy having only recently been sold.

From a consideration of the various books with which the Fund has been concerned, it

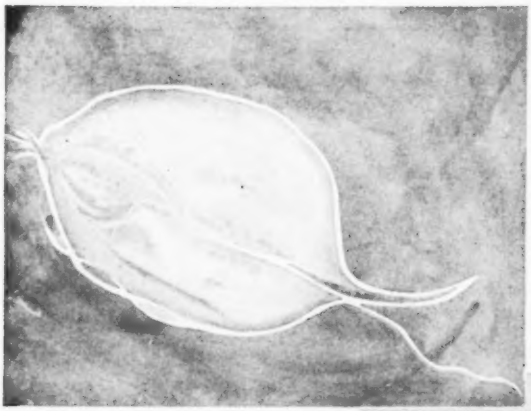
will be seen that the reason for the Fund's existence is to make possible the printing of scholarly works in the medical field which no publisher, forced to make ends meet, can afford to bring out. This it has done, with the success and variety of subject matter already shown, and it looks forward to making possible the publication of additional valuable works, particularly in historical medicine, as long as its resources hold out.

These will not last indefinitely, however, without replenishment. The character of the books administered by the Fund is necessarily of the sort which does not make a profit—or their sponsors would not have sought the Fund's aid. By the very nature of the undertaking, outlay is bound to exceed intake. And consequently the Fund will be able to sponsor fewer and fewer books as time goes on, unless friends of scholarship, of medicine, and of the Academy come forward occasionally to make up for this creeping recession. From time to time additional gifts have been made to the Fund by individuals interested in furthering the publication of a specific book or by others with general goodwill for the advancement of historical medical research. Contributions to the Library Publication Fund represent more than a single benefaction: they will be laid out for one worthy purpose, returning again and again to the fountain-head for re-investment in the spreading of knowledge. Any Fellow or friend of the Academy may be sure that a gift to this Fund will multiply its benefits to scholarship and its satisfaction to the giver many times over, and will at the same time be a lasting and tangible memorial to "Dr. Sam."

A RECENT LIBRARY PUBLICATION

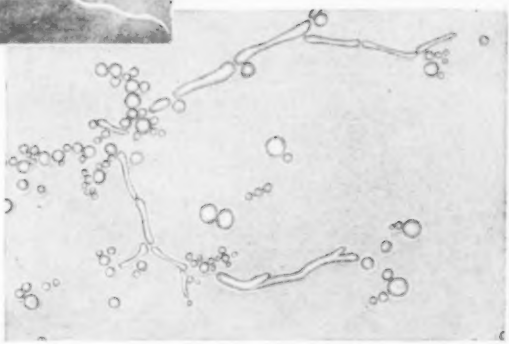
The Library Publication Fund Committee has just issued Dr. Judson B. Gilbert's *Bibliography of Articles on the History of American Medicine compiled from "Writings on American History,"* 1902-1937. This brings to light much medical material otherwise hidden in sources usually untapped by historians of medicine. The series published under the title of *Writings on American History* listed books and articles on the subject which appeared during the years 1902-1937 and consisted of forty-two volumes. Dr. Gilbert's index of the medical titles he culled from them supplements the "Bibliography of the History of Medicine of the United States and Canada," published annually in the *Bulletin of the History of Medicine* from 1940 on. Dr. Gilbert's bibliography is no. 9 of the Library's History of Medicine Series, and copies may be purchased for $1.25 in the Librarian's office.

PUBLICATIONS ARE TO BE OBTAINED FROM THE PUBLISHER, *NOT* FROM THE ACADEMY UNLESS OTHERWISE STATED.



Trichomonas vaginalis. One out of 5 women harbors this parasite.*

Monilia albicans.



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*Kuder, K.: Vaginal Infections, J. Am. M. Women's A. 5:173 (May) 1950.

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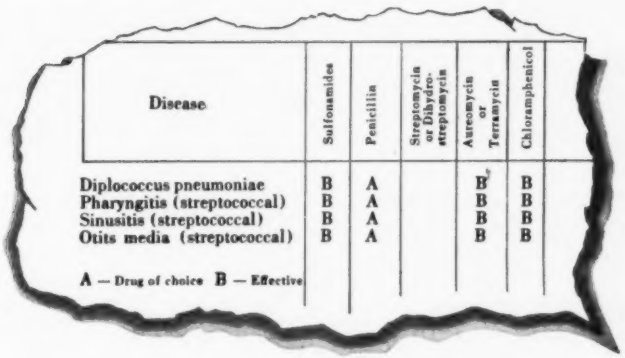

Disease	Sulfonamides	Penicillin	Streptomycin or Dihydrostreptomycin	Aureomycin or Terramycin	Chloramphenicol	
Diplococcus pneumoniae	B	A		B	B	
Pharyngitis (streptococcal)	B	A		B	B	
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*KEEFER, C. S., POSTGRAD. MED. 9:101, FEB. 1951

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*Not yet council accepted.

References: 1. Bedford, A.R.: J.A.M.A. 122:250 (1943)
2. Teloman, M.B.: Amer. Jrl. Obst. & Gyn. 46:346 (1943)

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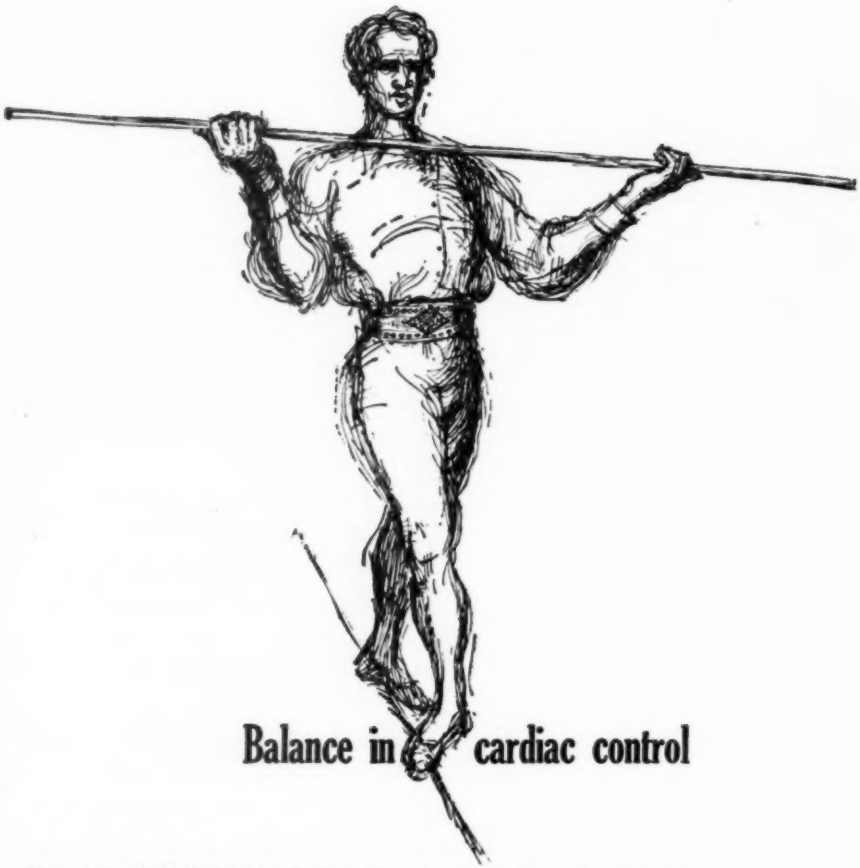

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1. *Schaaf, R. S., Hurst, J. W., and Williams C.: Med. Clin. North America (Mass. Gen. Hosp. No.) p. 1355 (Sept.) 1943.*

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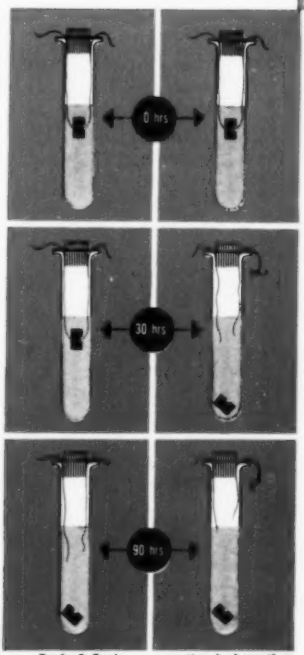

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1952

MARCH 6

1. MECHANISM AND MANAGEMENT OF CIRCULATORY FAILURE—William Dock, *Professor of Medicine, State University of New York at New York City, College of Medicine.*

MARCH 13

2. SHUNT OPERATIONS FOR THE TREATMENT OF PORTAL HYPERTENSION WITH SPECIAL REFERENCE TO CIRRHOSIS OF THE LIVER—Arthur H. Blakemore, *Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgeon, Presbyterian Hospital, New York.*

MARCH 20

3. DYNAMICS OF ACQUIRED VALVE LESIONS—Lewis Dexter, *Assistant Professor of Medicine, Harvard Medical School; Senior Associate in Medicine, Peter Bent Brigham Hospital.*

MARCH 27

4. LEPROSY—Frank C. Combs, *Professor of Dermatology and Syphilology, New York University Post-Graduate Medical School; Director of Dermatology and Syphilology, Bellevue Hospital; Member of Advisory Medical Board, Leonard Wood Memorial Hospital, (American Leprosy Foundation).*

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1. Hazelton Laboratories, Falls Church, Va. Private communication.
2. Nesbit and Lapides. Univ. Michigan Med. Bull. 16, 37-42 (1950).
3. Richardson and Rose. J. Urol. 63, 1113-19 (1950).
4. Robbins, Colby, Sosman and Eyler, Radiology 56, 684-688 (1951).
5. Neuhaus, Christman and Lewis. J. Lab. Clin. Med. 35, 43-9 (1950).

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Friday Afternoon, March 7, at 4:30 o'clock

RECENT CONTRIBUTIONS OF THE LABORATORY TO DIAGNOSIS AND THERAPY

Joseph C. Turner
Associate Professor of Clinical Medicine
Columbia University
Associate Visiting Physician, Presbyterian Hospital

Friday Afternoon, March 14, at 4:30 o'clock

RECENT ADVANCES IN THE MANAGEMENT OF THE POSTOPERATIVE PATIENT

Henry T. Randall
Clinical Director and Chief of Surgical Services
Memorial Center
Associate Professor of Surgery
Cornell University Medical School

Friday Afternoon, March 21, at 4:30 o'clock

RECENT ADVANCES IN DIETARY THERAPY IN HYPERTENSION AND ARTERIOSCLEROSIS

George A. Perera
Associate Professor of Medicine
College of Physicians and Surgeons
Columbia University

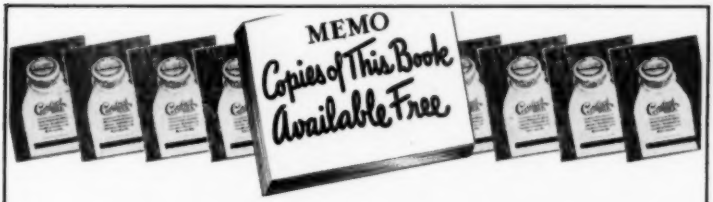
Friday Afternoon, March 28, at 4:30 o'clock

RECENT ADVANCES IN THE SURGICAL MANAGEMENT OF PEPTIC ULCER

Ralph Colp
Attending Surgeon, Mt. Sinai Hospital
Clinical Professor of Surgery, Columbia University

RECENT ADVANCES IN THE MEDICAL MANAGEMENT OF PEPTIC ULCER

Charles A. Flood
Assistant Clinical Professor of Medicine
Columbia University



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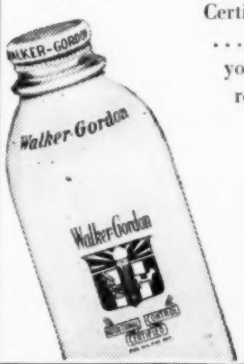

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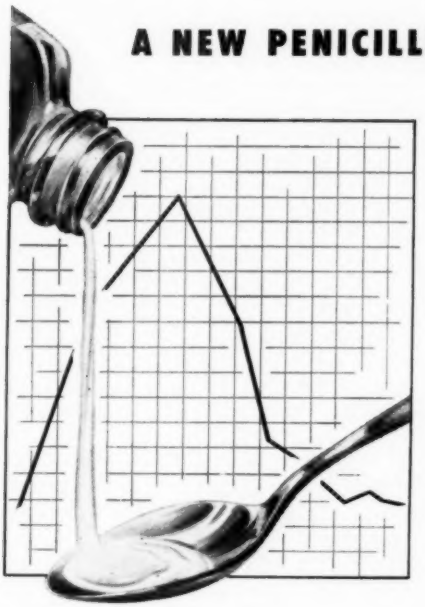

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1. Welch, H., and Putnam, L.E.: Personal communication
2. Lepper, M.H., and Dowling, H.F.: To be published
3. Preston, E., and Correll, L.F.: Personal communication

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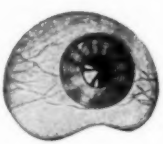

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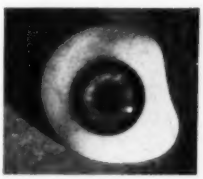

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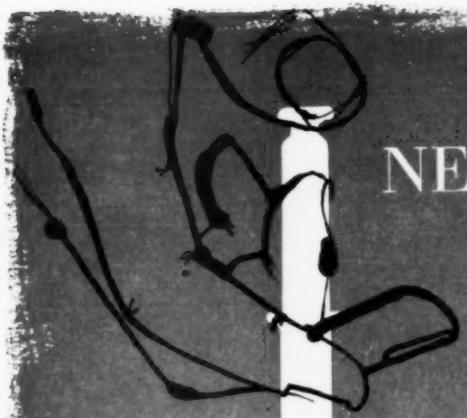

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Each drop of Crystalline Dihydrostreptomycin Sulfate Solution freely flows through a 22-gauge needle—at a touch of your finger tips.

This new preparation, derived from pure Crystalline Dihydrostreptomycin Sulfate, presents the ultimate in easy "syringeability": it is immediately ready for use—injection procedure is rapid and virtually effortless.

Each 2 cc. provides the equivalent of 1.0 Gm. of pure dihydrostreptomycin base.

Antibiotic Division **Pfizer** CHAS. PFIZER & CO., INC., *Brooklyn 6, N. Y.*

DAY

Each Dainite Day Tablet contains:

Sodium Pentobarbital	¼ gr.
Aminophylline	3 gr.
Ephedrine HCl	¼ gr.
Benzocaine	¼ gr.
Aluminum Hydroxide	2½ gr.

NITE

Each Dainite Nite Tablet contains:

Phenobarbital	⅜ gr.
Sodium Pentobarbital	½ gr.
Aminophylline	4 gr.
Benzocaine	¼ gr.
Aluminum Hydroxide	2½ gr.

Dainite Tablets provide day and night protection for the asthmatic patient, with almost complete absence of side-effects.[1] In a series of 100 patients with bronchial asthma and pulmonary emphysema receiving Dainite Tablets on arising and retiring, only 2 patients noted nausea[1] despite the daily, full therapeutic dose of aminophylline. Marked objective improvement of respiratory function, with significant relief of wheezing, dyspnea and cough, has been observed.[1]

DAINITE (Irwin-Neisler) provides a night and day difference in treatment that meets the requirements of the active and the resting patient. The use of antinausea factors safely permits a more effective, prolonged dosage of aminophylline than previously available in asthmatic preparations.

Supplied as the DAINITE UNIT containing 48 Day Tablets and 18 Nite Tablets in a unique dispensing unit . . . at prescription pharmacies everywhere. **Average Dose**: One Dainite (Day) Tablet t.i.d. before meals; one Dainite (Nite) Tablet at 10 P.M.

1. J.A.M.A. 147:730-737 (Oct. 20) 1951. Literature and detailed dosage information on request.

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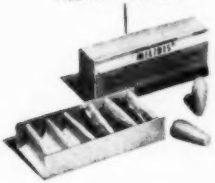

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